

1765-85956



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| (51) International Patent Classification 5 : C07C 311/18, 311/05, 311/29 C07K 5/06, A61K 37/64, 31/325 | A1 | (11) International Publication Number: WO 94/0449T (43) International Publication Date: 3 March 1994 (03.03.94) |
| (21) International Application Number: PCT/US93/07815 (22) International Filing Date: 25 August 1993 (25.08.93) (30) Priority data: 07/935,490 25 August 1992 (25.08.92) US (60) Parent Application or Grant (63) Related by Continuation US 07/935,490 (CIP) Filed on 25 August 1992 (25.08.92) (71) Applicants (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). THE MONSANTO COMPANY [US/US]; 800 North Lindbergh Boulevard, St. Louis, MO 63166 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): VAZQUEZ, Michael, L. [US/US]; 233 Saratoga Court, Gurnee, IL 60031 (US). MUELLER, Richard, A. [US/US]; 562 Stonegate Terrace, Glencoe, IL 60022 (US). TALLEY, John, J. [US/US]; 1510 Amisk Court, Chesterfield, MO 63017 (US). GETMAN, Daniel [US/US]; 66 Sunnyhill Court, Chesterfield, MO 63017 (US). DECRESCENZO, Gary, A. [US/US]; 536 Schrader Farm Drive, St. Peters, MO 63376 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). | | (74) Agents: UNGEMACH, Frank, S. et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). (81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: N-(ALKANOYLAMINO-2-HYDROXYPROPYL)-SULFONAMIDES USEFUL AS RETROVIRAL PROTEASE INHIBITORS (57) Abstract <p>Succinoylamino hydroxyethylamino sulfonamide compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.</p> | | |

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N-(ALKANOYLAMINO-2-HYDROXYPROPYL-)SULFONAMIDES USEFUL AS RETROVIRAL
PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

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1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for
10 inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and
15 for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

20 2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes
25 and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct
30 processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virions. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been
35 shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

10

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

20

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also disclose certain sulfamoyl-containing hydroxyethylamine renin inhibitors. EP O 264 795 also discloses certain sulfonamide-containing renin inhibitor compounds. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

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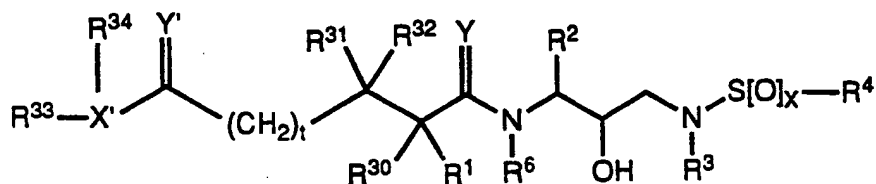
BRIEF DESCRIPTION OF THE INVENTION

5 The present invention is directed to virus
 inhibiting compounds and compositions. More particularly,
 the present invention is directed to retroviral protease
 inhibiting compounds and compositions, to a method of
 inhibiting retroviral proteases, to processes for
 10 preparing the compounds and to intermediates useful in
 such processes. The subject compounds are characterized
 as succinoylamino hydroxyethylamino sulfonamide inhibitor
 compounds.

DETAILED DESCRIPTION OF THE INVENTION

15 In accordance with the present invention, there
 is provided a retroviral protease inhibiting compound of
 the formula:

20



or a pharmaceutically acceptable salt, prodrug or ester
 thereof wherein:

25

x represents 0, 1 or 2;

t represents either 0 or 1;

30 R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃,
 -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂,
 -C(CH₃)₂(SH) -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃),
 -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and
 cycloalkyl radicals and amino acid side chains selected
 35 from asparagine, S-methyl cysteine and the corresponding

sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, phenylalanine, ornithine, alanine, histidine, norleucine, glutamine, valine, threonine, serine, o-alkyl serine,
5 aspartic acid, beta-cyano alanine, and allothreonine side chains;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally
10 substituted with a group selected from alkyl and halogen radicals, and -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals;

R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl,
15 cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from
20 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a
25 heterocycloalkyl or a heteroaryl radical;

X' represents N, O and C(R¹⁷) where R¹⁷ represents hydrogen and alkyl radicals;

30 Y and Y' independently represent O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³;

R⁴ represents radicals as defined by R³ except for hydrogen;

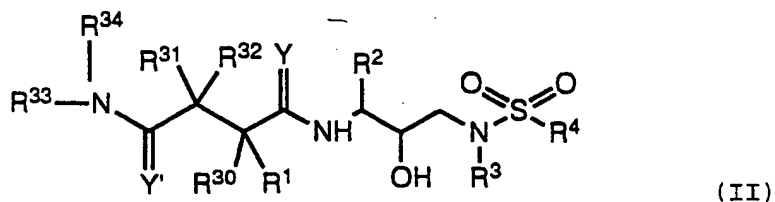
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R⁶ represents hydrogen and alkyl radicals as defined for R³;

R³⁰, R³¹ and R³² represent radicals as defined for R¹, or one of R¹ and R³⁰ together with one of R³¹ and R³² and the carbon atoms to which they are attached form a cycloalkyl radical; and

R³³ and R³⁴ independently represent hydrogen, radicals as defined for R³ or R³³ and R³⁴ together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R³⁴ is absent.

A preferred class of retroviral inhibitor compounds of the present invention are those represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof, preferably wherein the absolute stereochemistry about the hydroxy group is designated as (R);

R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, phenylalanine, ornithine, alanine, histidine, norleucine, glutamine, valine, threonine, serine, aspartic acid, beta-cyano alanine, and allothreonine side chains;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl, and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen

radicals; NO_2 , $-\text{C} \equiv \text{N}$, CF_3 , OR^9 and SR^9 wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

R^4 represents radicals as defined by R^3 except for hydrogen;

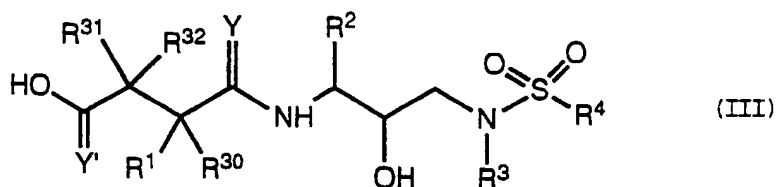
R^{30} , R^{31} and R^{32} represent radicals as defined for R^1 , or one of R^1 and R^{30} together with one of R^{31} and R^{32} and the carbon atoms to which they are attached form a cycloalkyl radical; and

R^{33} and R^{34} independently represent hydrogen, radicals as defined for R^3 or R^{33} and R^{34} together with the nitrogen atom to which they are attached represent heterocycloalkyl and heteroaryl radicals;

Y and Y' independently represent O, S, and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3 . Preferably, Y and Y' represent O.

Yet another preferred class of compounds are those represented by the formula:

35



or a pharmaceutically acceptable salt, prodrug or ester thereof, preferably wherein the stereochemistry about the hydroxy group is designated as R, wherein Y, Y', R¹, R², R³, R⁴, R³⁰, R³¹ and R³² are as defined above with respect to Formula (II). Preferably, Y and Y' represent O.

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10, preferably from 1 to about 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to about 18 carbon atoms preferably from 2 to about 8 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl and the like. The term alkynyl, alone or in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and containing from 2 to about 10 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, propargyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a

cycloalkyl radical containing from about 3 to about 8, preferably from about 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The

5 term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-

10 butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as

15 benzyl, 2-phenylethyl and the like. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula $-C(O)-O-aralkyl$ in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term

20 "aryloxy" means a radical of the formula $aryl-O-$ in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl,

25 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused

30 monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted

35 alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl" means an acyl radical derived from

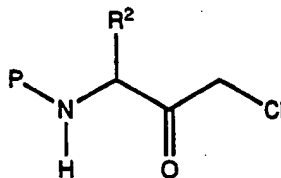
an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 5 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The heterocyclyl or heterocycloalkyl portion of a 10 heterocyclylcarbonyl, heterocyclylloxycarbonyl, heterocyclylalkoxycarbonyl, or heterocyclylalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, 15 oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by 20 oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaryl, heteroarylloxycarbonyl, or a heteroaralkoxy carbonyl group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and 25 is optionally substituted as defined above with respect to the definition of heterocyclyl. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 30 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl 35 (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, β -carbolinyl, 2-benzofurancarbonyl, 1-,2-,4- or

5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the
5 significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclyloxycarbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein
10 heterocyclyl is as defined above. The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylalkoxycarbonyl" means an acyl radical derived
15 from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term
20 "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl,
25 aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from
30 hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol
35 or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable, to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. An N-protected chloroketone derivative of an amino acid having the formula:



25

wherein P represents an amino protecting group, and R² is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, butyryl, t-butoxycarbonyl, acetyl, benzoyl and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from

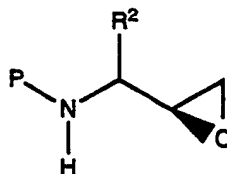
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-10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available e.g. such as from
5 Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

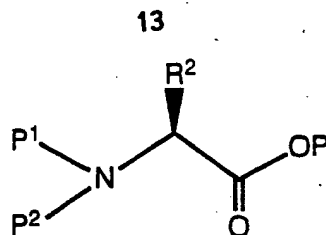
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The halo alcohol can be used directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino
15 epoxide of the formula:



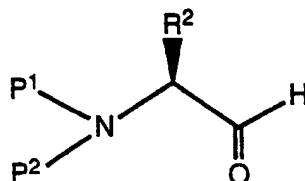
wherein P and R² are as defined above. Suitable solvent
20 systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium
25 t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared starting with an L-amino acid which is reacted
30 with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P¹ and P² independently represent hydrogen, benzyl and amino-protecting groups as defined above with respect to P, provided that P¹ and P² are not both hydrogen; P³ represents a carboxyl protecting group such as methyl, ethyl, tertiary-butyl, benzyl, and the like, and R² is as defined above.

10 The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. The resulting alcohol is then
15 converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:

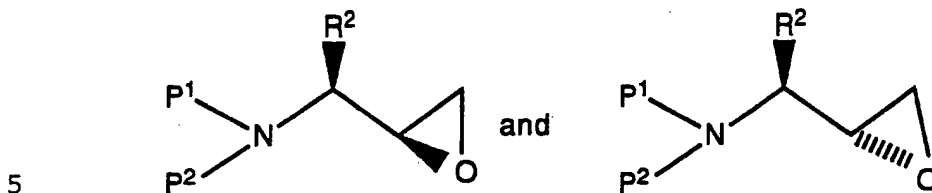


20 wherein P¹, P² and R² are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

25

The aldehyde resulting from the Swern oxidation is then reacted with a halomethyl lithium reagent, which reagent is generated in situ by reacting an alkyl lithium or aryl lithium compound with a dihalomethane represented
30 by the formula X¹CH₂X² wherein X¹ and X² independently represent I, Br or Cl. For example, a solution of the aldehyde and chloriodomethane in THF is cooled to -78° C

and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



The diastereomers can be separated, e.g., by chromatography or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

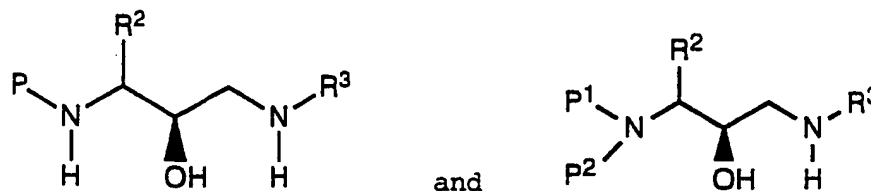
The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula:



wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux.

Suitable solvent systems include protic, non-protic and dipolar aprotic solvents, such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative

(hereinafter referred to as an amino alcohol) can be represented by the formulas:



5

wherein P, P¹, P², R² and R³ are as described above.

Alternatively, a haloalcohol can be utilized in place of the amino epoxide,

10

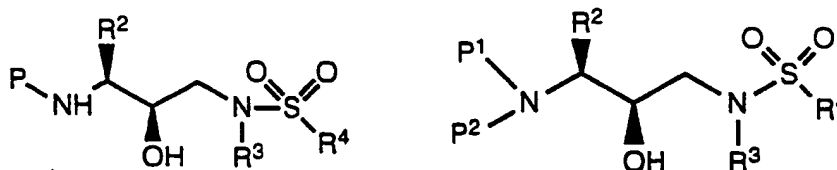
The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride (R⁴SO₂Cl) or sulfonyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran and the like. Suitable acid scavengers include

15

triethylamine, pyridine and the like. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented, depending on the epoxide

20

utilized by the formulas:



wherein P, P¹, P², R², R³ and R⁴ are as defined above.

25

The sulfonyl halides of the formula R⁴SO₂X can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfuryl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic

30

acids may be converted to sulfonyl halides using reagents such as PCl_5 , and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Such

5 sulfonic acids are also commercially available.

In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the $-\text{SO}_2-$ moiety is replaced by

10 an $-\text{SO}-$ or $-\text{S}-$ moiety, respectively.

Following preparation of the sulfonamide derivative, the amino protecting group P or P^1 and P^2 is removed under conditions which will not affect the

15 remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium

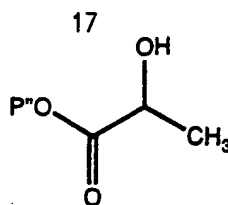
20 on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent

25 system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Where the protecting group is a benzyl radical, it can be removed by hydrogenolysis. Following neutralization of the salt, the amine is then reacted with a succinic acid

30 as described below

To produce the succinic acid portion of the compounds of Formula I, the starting material is a lactate of the formula:

35

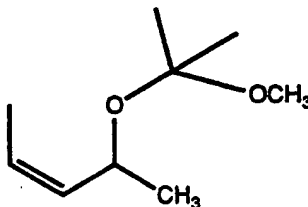


wherein P⁺ represents alkyl and aralkyl radicals, such as, for example, ethyl, methyl, benzyl and the like. The

5 hydroxyl group of the lactate is protected as its ketal by reaction in a suitable solvent system with methyl isopropenyl ether (1,2-methoxypropene) in the presence of a suitable acid. Suitable solvent systems include

10 methylene chloride, tetrahydrofuran and the like as well as mixtures thereof. Suitable acids include POCl₃ and the like. It should be noted that well-known groups other than methyl isopropenyl ether can be utilized to form the ketal. The ketal is then reduced with diisobutylaluminum

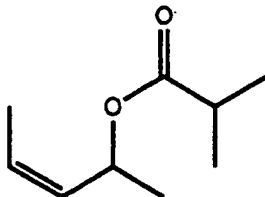
15 hydride (DIBAL) at -78°C to produce the corresponding aldehyde which is then treated with ethylidene triphenylphosphorane (Wittig reaction) to produce a compound represented by the formula:



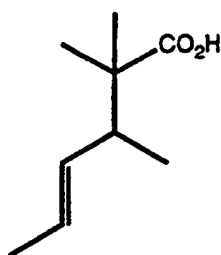
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The ketal protecting group is then removed utilizing procedures well-known in the art such as by mild acid hydrolysis. The resulting compound is then

25 esterified with isobutyryl chloride to produce a compound of the formula:



This compound is then treated with lithium diisopropyl amide at -78°C followed by warming of the reaction mixture to room temperature to effect a Claisen rearrangement ([3,3]) to produce the corresponding acid
5 represented by the formula:

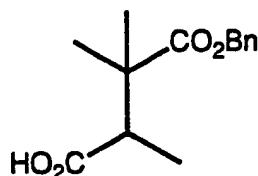


Those skilled in the art will recognize that
10 variations on this scheme are possible, using either different protecting groups or reagents to carry out the same transformations. One can also utilize other acid chlorides in place of isobutyryl chloride to prepare similar analogs.

15

Treatment of the acid with benzyl bromide in the presence of a tertiary amine base, e.g., DBU, produces the corresponding ester which is then cleaved oxidatively to give a trisubstituted succinic acid:

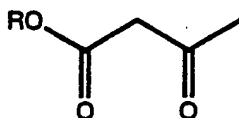
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The trisubstituted succinic acid is then coupled to the sulfonamide isostere utilizing procedures well
25 known in the art. To produce the free acid, the benzyl ester is removed by hydrogenolysis to produce the corresponding acid. The acid can then be converted to the primary amide by methods well-known in the art. The resulting product is a compound represented by Formula I.

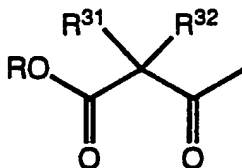
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An alternative method for preparing trisubstituted succinic acids involves reacting an ester of acetoacetic acid represented by the formula:

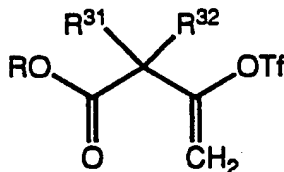


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where R is a suitable protecting group, such as methyl, ethyl, benzyl or t-butyl with sodium hydride and a hydrocarbyl halide (R^{31}X or R^{32}X) in a suitable solvent, e.g., THF, to produce the corresponding disubstituted derivative represented by the formula:



15 This disubstituted acetoacetic acid derivative is then treated with lithium diisopropyl amide at about -10°C and in the presence of $\text{PhN}(\text{triflate})_2$ to produce a vinyl triflate of the formula:

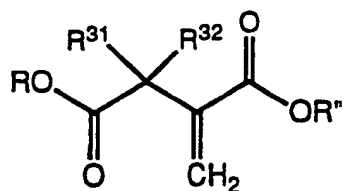


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The vinyl triflate is then carbonylated utilizing a palladium catalyst, e.g., $\text{Pd}(\text{OAc})_2$ and Ph_3P , in the presence of an alcohol ($\text{R}''\text{OH}$) or water ($\text{R}''=\text{H}$) and a base, e.g., triethylamine, in a suitable solvent such as DMF, to produce the olefinic ester or acid of the formula:

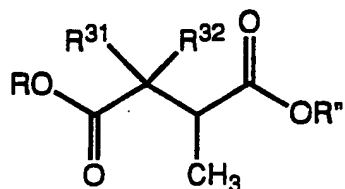
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20



The olefin can then be subsequently asymmetrically hydrogenated, as described below, to produce a

5 trisubstituted succinic acid derivative of the formula:

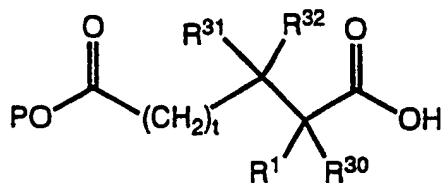


If R'' is not H, R'' can be removed by either hydrolysis, acidolysis, or hydrogenolysis, to afford the corresponding

10 acid, which is then coupled to the sulfonamide isostere as described above and then, optionally, the R group removed to produce the corresponding acid, and optionally, converted to the amide.

15

Alternatively, one can react the sulfonamide isostere with either a suitably monoprotected succinic acid or glutaric acid of the following structure;



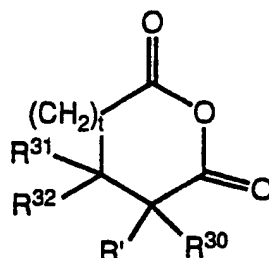
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followed by removal of the protecting group and conversion of the resulting acid to an amide. One can also react an

anhydride of the following structure;

25

21



with the sulfonamide isostere and then separate any
isomers or convert the resulting acid to an amide and then
5 separate any isomers.

It is contemplated that for preparing compounds
of the Formulas having R^6 , the compounds can be prepared
following the procedure set forth above and, prior to
10 coupling the sulfonamide derivative to the succinic acid
portion of the molecule carried through a procedure
referred to in the art as reductive amination. Thus, a
sodium cyanoborohydride and an appropriate aldehyde or
ketone can be reacted with the sulfonamide derivative
15 compound or appropriate analog at room temperature in
order to reductively aminate any of the compounds of
Formulas I-III. It is also contemplated that where R^3 of
the amino alcohol intermediate is hydrogen, the inhibitor
compounds can be prepared through reductive amination of
20 the final product of the reaction between the amino
alcohol and the amine or at any other stage of the
synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas
25 set forth above for the antiviral compounds and
derivatives as well as the intermediates are compounds
otherwise corresponding thereto and having the same
general properties wherein one or more of the various R
groups are simple variations of the substituents as
30 defined therein, e.g., wherein R is a higher alkyl group
than that indicated. In addition, where a substituent is
designated as, or can be, a hydrogen, the exact chemical

nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

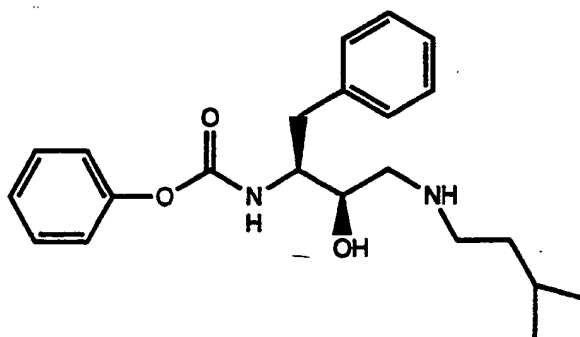
The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

5

Example 1



10

Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

PART A:

15 To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred
20 minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium
25 chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids
30 were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate

and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+ = 340$.

5 PART B:

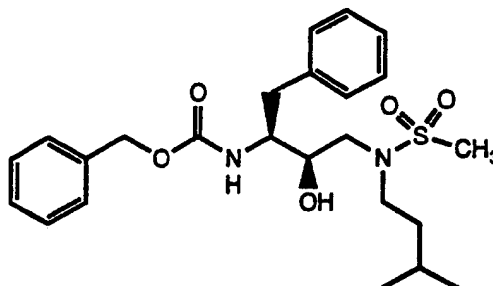
To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After
10 stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from
15 hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and $MH^+ 298$.

Part C:

20

19.9 equivalents) in 90 mL of isopropyl alcohol was heated to reflux for 3.1h. The solution was cooled to room temperature and partially concentrated in vacuo and the remaining solution poured
25 into 200 mL of stirring hexanes whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 11.76 g, 79% of N[(3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine, mp 118-122° C, FAB MS: $MH^+=385$.

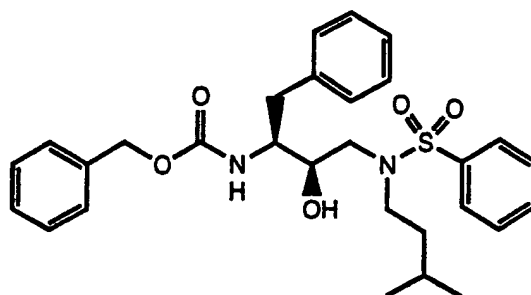
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Example 2

5 Preparation of phenylmethyl [2R-hydroxy-3-[(3-
10 methylbutyl) (methanesulfonyl)amino]-1S-
15 (phenylmethyl)propyl]carbamate

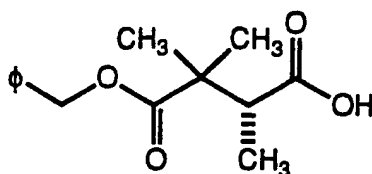
To a solution of N[3(S)-benzyloxycarbonylamino-
10 2(R)-hydroxy-4-phenylbutyl] N-isoamylamine from
Example 1, Part C (2.0 gm, 5.2 mmol) and triethylamine
(723 uL, 5.5 mmol) in dichloromethane (20 mL) was added
dropwise methanesulfonyl chloride (400 uL, 5.2 mmol).
The reaction mixture was stirred for 2 hours at room
15 temperature, then the dichloromethane solution was
concentrated to ca. 5 mL and applied to a silica gel
column (100 gm). The column was eluted with chloroform
containing 1% ethanol and 1% methanol. The phenylmethyl

20 [2R-hydroxy-3-[(3-methylbutyl) (methanesulfonyl)amino]-1S-
(phenylmethyl)propyl]carbamate was obtained as a white
solid Anal. Calcd for C₂₄H₃₄N₂O₅S: C, 62.31; H, 7.41; N,
6.06. Found: C, 62.17; H, 7.55; N, 5.97.

Example 3

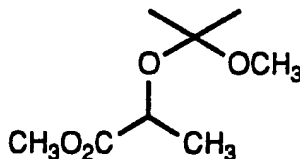
5 Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

- 10 From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine from Example 1, Part C (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.
- 15 Column chromatography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for C₂₉H₃₆N₂O₅S: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

Example 45 Preparation of Benzyl 2,2,3(R)-trimethylsuccinate

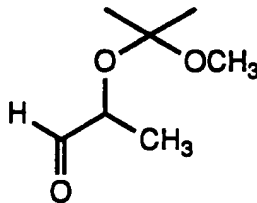
PART A: Preparation of Methyl (S)-lactate, 2-methoxy-2-propyl ether.

10



To a mixture of methyl (S)-(-)-lactate (13.2g, 100 mmol) and, 2-methoxypropene (21.6g, 300 mmol) in CH₂Cl₂ (150 ml) was added POCl₃ (7 drops) at r.t. and the resulting mixture was stirred at this temperature for 16 hours. After the addition of Et₃N (10 drops), the solvents were removed in vacuo to give 20.0g of (98%) desired product.

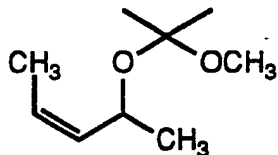
20 PART B: Preparation of 2(S)-hydroxypropanal, 2-methoxy-2-propyl ether.



25 To a solution of compound from Part A (20.0g) in CH₂Cl₂ (100 ml) was added DIBAL (65 ml of 1.5M solution in toluene, 97.5 mmol) dropwise at -78°C for 45

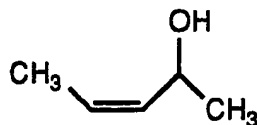
min., then stirring was continued at this temperature for another 45 min. To this cold solution was added MeOH (20 ml), saturated NaCl solution (10 ml) and allowed the reaction mixture to warm up to r.t. and diluted with
5 ether (200 ml), MgSO₄ (150g) was added and stirred for another 2 h. The mixture was filtered and the solid was washed twice with ether. The combined filtrates were rotavaped to afford 11.2g (78%) of the desired aldehyde.

10 PART C: Preparation of 2(S)-hydroxy-cis-3-butene, 2-methoxy-2-propyl ether.



15 To a suspension of ethyltriphenylphosphonium bromide (28g, 75.5 mmol) in THF (125 ml) was added KN (TMS)₂ (15.7g, 95%, 75 mmol) in portions at 0°C and stirred for 1 h at the temperature. This red reaction mixture was cooled to -78°C and to this was added a
20 solution of aldehyde from Part B (11g, 75 mmol) in THF (25 ml). After the addition was completed, the resulting reaction mixture was allowed to warm up to r.t. and stirred for 16 h. To this mixture was added saturated NH₄Cl (7.5 ml) and filtered through a pad of celite with
25 a thin layer of silica gel on the top. The solid was washed twice with ether. The combined filtrates were concentrated in vacuo to afford 11.5g of crude product. The purification of crude product by flash chromatography (silica gel, 10:1 Hexanes/EtoAc) affording 8.2g (69%)
30 pure alkene.

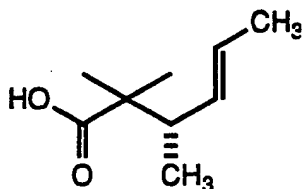
PART D: Preparation of 2(S)-hydroxy-cis-3-butene.



5 A mixture of alkene from Part C (8.2g) and 30% aqueous acetic acid (25 ml) was stirred at r.t. for 1 hour. To this mixture was added NaHCO₃ slowly until the pH was ~ 7, then extracted with ether (10 ml x 5). The combined ether solutions were dried (Na₂SO₄) and
10 filtered. The filtrate was distilled to remove the ether to give 2.85g (64%) pure alcohol, m/e=87(M+H).

PART E: Preparation of 2,2,3-trimethyl-hex-(trans)-4-enoic acid.

15

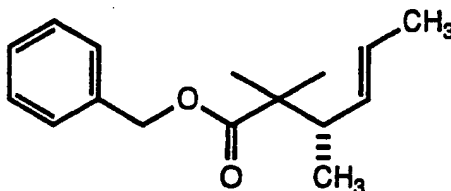


To a mixture of alcohol from Part D (2.5g, 29 mmol) and pyridine (2.5 ml) in CH₂Cl₂ (60 ml) was added
20 isobutyryl chloride (3.1g, 29 mmol) slowly at 0°C. The resulting mixture was stirred at r.t. for 2 hours then washed with H₂O (30 ml x 2) and sat. NaCl (25 ml). The combined organic phases were dried (Na₂SO₄), concentrated to afford 4.2g (93%) ester 2(S)-hydroxy-cis-3-butenyl
25 isobutyrate. This ester was dissolved in THF (10 ml) and was added to a 1.0M LDA soln. (13.5 ml of 2.0M LDA solution in THF and 13.5 ml of THF) slowly at -78°C. The resulting mixture was allowed to warm up to r.t. and stirred for 2 h and diluted with 5% NaOH
30 (40 ml). The organic phase was separated, the aqueous phase was washed with Et₂O (10 ml). The aqueous solution was collected and acidified with 6N HCl to pH ~ 3. The

mixture was extracted with ether (30 ml x 3). The combined ether layers were washed with sat. NaCl (25 ml), dried (Na₂SO₄) and concentrated to afford 2.5g (60%) of desired acid, m/e=157(M+H).

5

PART F: Preparation of benzyl 2,2,3(S)-trimethyl-trans-4-hexenoate.

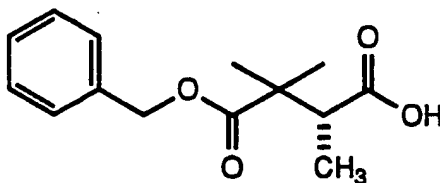


10

A mixture of acid from Part E (2.5g, 16 mmol), BnBr (2.7g, 15.8 mmol), K₂CO₃ (2.2g, 16 mmol), NaI (2.4g) in acetone (20 ml) was heated at 75°C (oil bath) for 16 h. The acetone was stripped off and the residue was dissolved in H₂O (25 ml) and ether (35 ml). The ether layer was separated, dried (Na₂SO₄) and concentrated to afford 3.7g (95%) of benzyl ester, m/e=247(M+H).

PART G: Preparation of benzyl 2,2,3(R)-trimethylsuccinate.

20



To a well-stirred mixture of KMnO₄ (5.4g, 34, 2 mmol), H₂O (34 ml), CH₂Cl₂ (6 ml) and benzyltriethylammonium chloride (200 mg) was added a solution of ester from Part F (2.1g, 8.54 mmol) and acetic acid (6 ml) in CH₂Cl₂ (28 ml) slowly at 0°C. The resulting mixture was stirred at the temperature for 2 h then r.t. for 16 h. The mixture was cooled in an ice-water bath, to this was added 6N HCl (3 ml) and solid

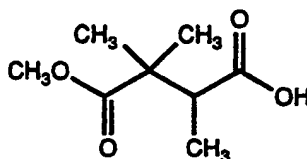
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- NaHSO₃ in portions until the red color disappeared. The clear solution was extracted with CH₂Cl₂ (30 ml x 3). The combined extracts were washed with sat. NaCl solution, dried (Na₂SO₄) and concentrated to give an oil.
- 5 This oil was dissolved in Et₂O (50 ml) and to this was added sat. NaHCO₃ (50 ml). The aqueous layer was separated and acidified with 6N HCl to pH ~ 3 then extracted with Et₂O (30 ml x 3). The combined extracts
- 10 were washed with sat. NaCl solution (15 ml), dried (Na₂SO₄) and concentrated to afford 725 mg (34%) of desired acid, benzyl 2,2,3(R)-trimethylsuccinate, m/e=251(M+H).

Example 5

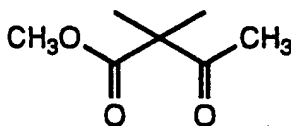
15



Preparation of methyl 2,2-dimethyl-3-methyl succinate, (R) and (S) isomers.

20

PART A: Preparation of methyl 2,2-dimethyl-3-oxo-butanoate.

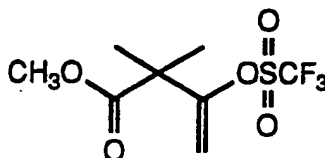


25

- A 250 ml RB flask equipped with magnetic stir bar and N₂ inlet was charged with 100 ml dry THF and 4.57g (180 mmol) of 95% NaH. The slurry was cooled to -20°C and 10g (87 mmol) methyl acetoacetate was added
- 30 dropwise followed by 11.3 ml (181 mmol) CH₃I. The reaction was stirred at 0°C for 2 hours and let cool to room temperature overnight. The reaction was filtered to remove NaI and diluted with 125 ml Et₂O. The organic

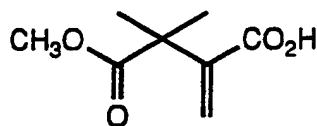
phase was washed with 1x100 mL 5% brine, dried and concentrated in vacuo to a dark golden oil that was filtered through a 30g plug of silica gel with hexane. Concentration in vacuo yielded 10.05g of desired methyl ester, as a pale yellow oil, suitable for use without further purification.

PART B: Preparation of methyl 2,2-dimethyl-3-oxo-(trifluoromethanesulfonate)-but-3-enoate.



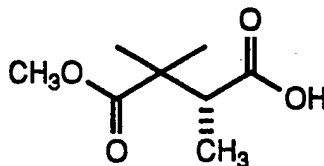
A 250 mL RB flask equipped with magnetic stir bar and N₂ inlet was charged with 80 mL THF and 5.25 mL (37.5 mmol) diisopropylamine was added. The solution was cooled to -25°C (dry ice/ethylene glycol) and 15 mL (37.5 mmol) of 2.5 M n-BuLi in hexanes was added. After 10 minutes a solution of 5g (35 mmol) 1 in 8 mL dry THF was added. The deep yellow solution was stirred at -20°C for 10 min. then 12.4g N-phenyl bis(trifluoromethanesulfonimide) (35 mmol) was added. The reaction was stirred @ -10°C for 2 hours, concentrated in vacuo and partitioned between ethyl acetate and sat. NaHCO₃. The combined organic phase was washed with NaHCO₃, brine and conc. to an amber oil that was filtered through a 60g silica gel plug with 300 mL 5% ethyl acetate/hexane. Conc. in vacuo yielded 9.0g light yellow oil that was diluted with 65 mL ethyl acetate and washed with 2x50 mL 5% aq K₂CO₃, 1x10 mL brine, dried over Na₂SO₄ and conc. in vacuo to yield 7.5g (87%) vinyl triflate, (m/e=277(M+H)) suitable for use without further purification.

PART C: Preparation of methyl 2,2-dimethyl-3-carboxyl-but-3-enoate.



A 250 ml Fisher Porter bottle was charged with
5 7.5g (27 mmol) of compound prepared in B, 50 ml dry DMF,
360 mg (1.37 mmol) triphenyl phosphine and 155 mg (.69
mmol) Pd(II)(OAc)₂. The reaction mixture was purged
twice with N₂ then charged with 30 psi CO. Meanwhile a
solution of 20 ml dry DMF and 7.56 ml (54 mmol) NEt₃ was
10 cooled to 0°C to this was added 2.0g (43 mmol) of 99%
formic acid. The mixture was swirled and added to the
vented Fisher Porter tube. The reaction vessel was
recharged to 40 psi of CO and stirred 6 hours @ room
temperature. The reaction mixture was concentrated in
15 vacuo and partitioned between 100 mL of ethyl acetate and
75 mL 5% aq K₂CO₃. The aqueous phase was washed with
1x40 mL additional ethyl acetate and then acidified with
conc. HCl/ice. The aqueous phase was extracted with 2x70
mL of ethyl acetate and the organics were dried and conc.
20 to yield 3.5g (75%) white crystals, mp 72-75°C,
identified as the desired product (m/e=173 (M+H)).

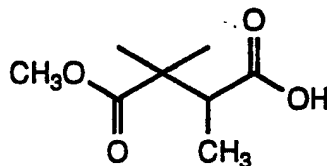
PART D: Preparation of methyl 2,2-dimethyl-3-
25 methylsuccinate, isomer #1.



A steel hydrogenation vessel was charged with
30 510 mg (3.0 mmol) acrylic acid, from Part C, and 6 mg Ru
(acac)₂ (R-BINAP) in 10 ml degassed MeOH. The reaction
was hydrogenated at 50 psi/room temperature for 12 hours.
The reaction was then filtered through celite and conc.

to 500 mg clear oil which was shown to be a 93:7 mixture of isomer #1 and #2, respectively as determined by GC analysis using a 50 M β -cyclodextrin column: 150°C - 15 min. then ramp 2°C/min.; isomer #1, 17.85 min., isomer
5 #2, 18-20 min.

PART E: Preparation of methyl 2,2-dimethyl-3-methylsuccinate, Isomer #2.



10

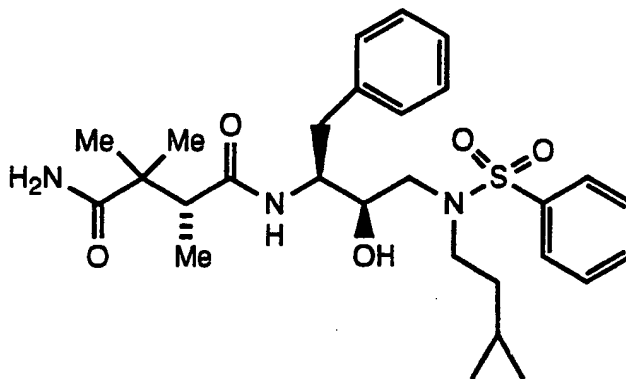
A steel hydrogenation vessel was charged with 500 mg (2.9 mmol) acrylic acid, Part C, and 6 mg Ru(OAc)(acac) (S-BINAP) in 10 ml degassed MeOH. The reaction was
15 hydrogenated at 50 psi/room temperature for 10 hours. The reaction was filtered through celite and concentrated in vacuo to yield 490 mg of product as a 1:99 mixture of isomers #1 and #2, respectively, as determined by chiral GC as above.

20

In a similiar manner, one can use benzyl 2,2-dimethyl-3-oxo-butanoate to prepare benzyl 2,2,3-trimethylsuccinate, R and S isomers. Other methods for preparing succinic acids, succinates and succinamides are
25 well known in the art and can be utilized in the present invention.

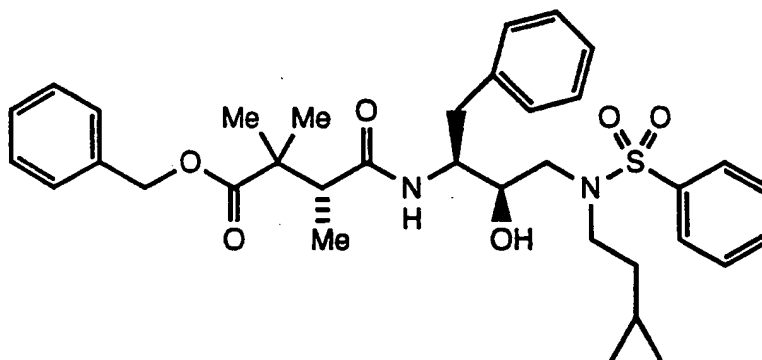
Example 6

Preparation of Butanediamide, N⁴-[2-hydroxy-3-
 [(3-methylbutyl) (phenylsulfonyl) amino]-1-
 5 (phenylmethyl)propyl]-2,2,3-Trimethyl-, [1S-
 [1R*(S*), 2S*]]-.

10 PART A:

Preparation of Butanoic acid, 4-[[2-hydroxy-3-
 [(3-methylbutyl) (phenylsulfonyl) amino]-1-
 (phenylmethyl)propyl]amino]-2,2,3-Trimethyl-4-oxo,
 phenylmethyl ester, [1S-[1R*(S*), 2S*]]-

15



A solution of 10.1 g (19.3 mmol) of phenylmethyl[2R-
 hydroxy-3-[(3-methylbutyl) (phenylsulfonyl) amino]-1S-
 20 (phenylmethyl)propyl]carbamate from Example 3 in 40 mL of
 methanol was hydrogenated over 2 g of 10% palladium-on-
 carbon under 50 psig of hydrogen for six hours. After
 flushing with nitrogen, the catalyst was removed by

filtration through celite and the filtrate concentrated to provide 7.41 g (99%) of 2(R)-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl, amino)-1(S)-(phenylmethyl)propylamine.

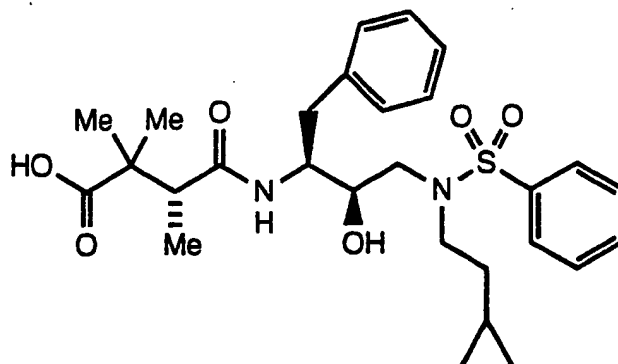
- 5 To a solution of 2.5 g (10.0 mmol) of benzyl 2,2,3(R)-trimethylsuccinate and 2.1 g (15.0 mmol) of N-hydroxybenzotriazole in 10 mL of anhydrous N,N-dimethylformamide (DMF) at 0°C, was added 2.1 g
10 (11.0 mmol) of 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). After two hours, a solution of 3.9 g (10.0 mmol) of 2(R)-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propylamine in 3 mL of DMF was added.
15 After stirring at room temperature for sixteen hours, the solvent was removed under reduced pressure, the residue dissolved in ethyl acetate and then washed with 0.2 N citric acid, 5% aqueous sodium bicarbonate, saturated brine, dried over anhydrous magnesium sulfate, filtered
20 and concentrated to afford 5.74 g of crude product. This was chromatographed over silica gel using 1% methanol/methylene chloride as eluent ($R_f=0.08$) to afford 3.87 g (62% yield) of the desired product, $m/e = 533(M+H^+)$.

25

PART B:

- Preparation of Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-[1S-
30 [1R*(S*),2S*]]-.

37



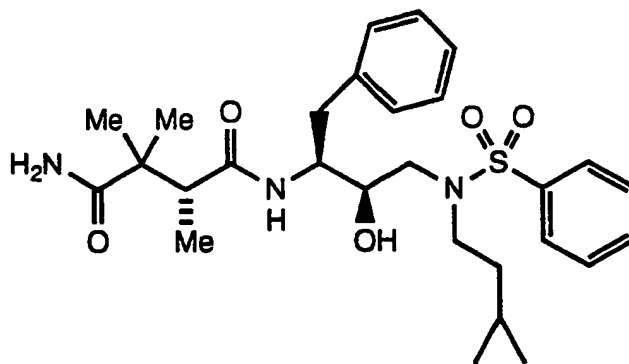
A solution of 3.87 g (6.21 mmol) of benzyl ester from part A in 40 mL of ethanol was hydrogenated over 1.5 g of 10% palladium-on-carbon under 50 psig of hydrogen for four hours. After flushing with nitrogen, the catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to afford 3.24g (98%) of desired product.

10

PART C:

Preparation of Butanediamide, N⁴-[2-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amine]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*),2S*]]-.

15



To a solution of 3.24 g (6.1 mmol) of acid from part B and 1.86 g (12.2 mmol) of N-hydroxybenzotriazole in 6 mL of anhydrous DMF at 0°C was added 1.75 g (9.1 mmol) of EDC. After stirring at 0°C for two hours, 3.44 g (60.8 mmol) of 30% aqueous ammonia was added. After stirring

20

at room temperature for twenty hours, the solvents were removed under reduced pressure, the residue dissolved in ethyl acetate and then washed with 0.2 N citric acid, 5% aqueous sodium bicarbonate, saturated brine, dried over 5 anhydrous magnesium sulfate, filtered and concentrated to afford 3.75g of crude material. This was passed through a column of 150 g of basic alumina with 20:1 (v:v) methylene chloride/methanol to remove unreacted acid. The resulting product was precipitated from methylene 10 chloride with hexane to afford 2.1 g (65%) of the desired product, m.p. 110°-112°C, m/e = 538 (m+Li).

Example 7

15 In a manner analogous to that of the previous examples, the compounds listed in Table 1 were prepared.

Table 1

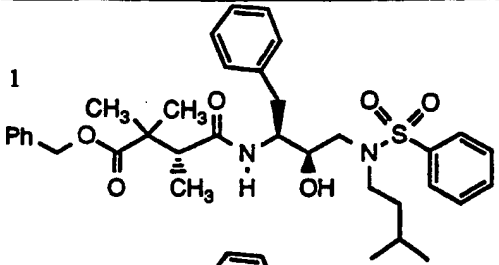
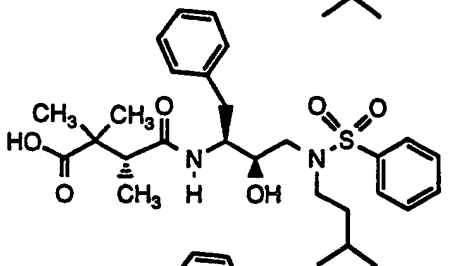
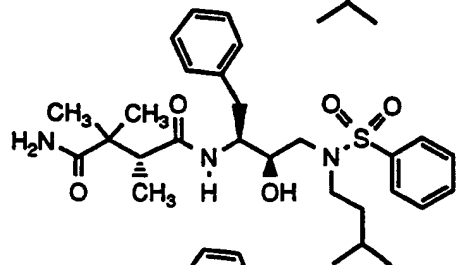
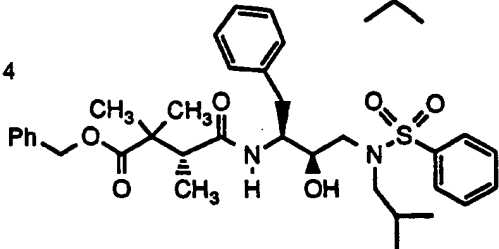
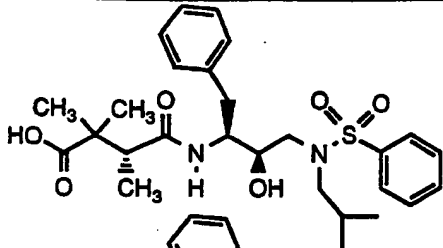
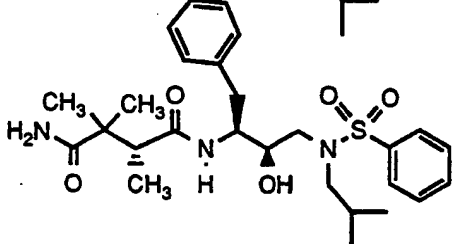
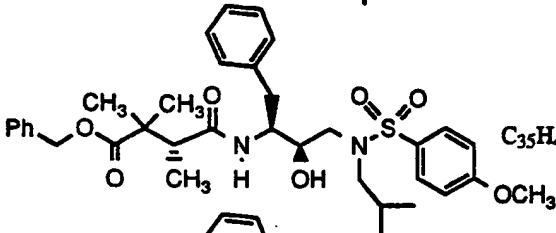
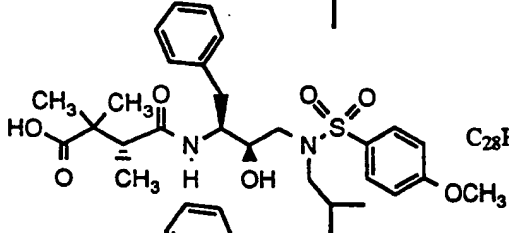
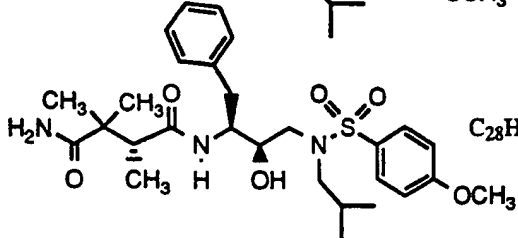
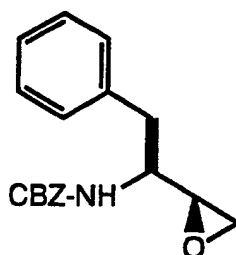
| Entry | COMPOUND | Mass Determination | | |
|-------|---|-----------------------|-----------|-------|
| | | Formula | Calcd | Found |
| 1 |  | $C_{35}H_{46}O_6N_2S$ | 623(M+H) | 623 |
| 2 |  | $C_{28}H_{40}O_6N_2S$ | 539(M+Li) | 539 |
| 3 |  | $C_{28}H_{41}O_5N_3S$ | 538(M+Li) | 538 |
| 4 |  | $C_{34}H_{44}O_6N_2S$ | 615(M+Li) | 615 |

Table 1
(continued)

| 5 | Entry | COMPOUND | Mass Determination | | |
|---|-------|---|-----------------------|-----------|-------|
| | | | Formula | Calcd | Found |
| | 5 |  | $C_{27}H_{38}O_6N_2S$ | 525(M+Li) | 525 |
| | 6 |  | $C_{27}H_{39}O_5N_3S$ | 524(M+Li) | 524 |
| | 7 |  | $C_{35}H_{46}O_7N_2S$ | 645(M+Li) | 645 |
| | 8 |  | $C_{28}H_{40}O_7N_2S$ | 549(M+H) | 549 |
| | 9 |  | $C_{28}H_{41}O_6N_3S$ | 548(M+H) | 548 |

Example 8

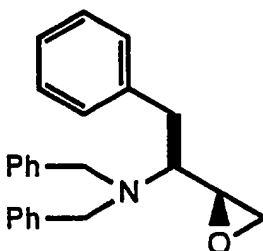
Additional exemplary compounds of the present invention are listed in Tables 2-7. These compounds could be prepared in a manner analogous to the above Examples and according to the following general procedures.

General Procedure for the Synthesis of Amino EpoxidePART A:

To a solution of 0.226 mol of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C , is added 1.54 equiv. of solid sodium borohydride over one hundred minutes. The solvents are then removed under reduced pressure at 40°C and the residue is dissolved in ethyl acetate (approx. 1L). The solution is washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and is then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution is removed under reduced pressure. To the resulting oil is added hexane (approx. 1L) and the mixture is warmed to 60°C with swirling. After cooling to room temperature, the solids are collected and washed with 2L of hexane. The resulting solid is recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp $150-151^{\circ}\text{C}$ and $M+Li^{+} = 340$.

PART B:

To a solution of 1.2 equiv. of potassium hydroxide in 968 mL of absolute ethanol at room temperature, is added 0.097 mol of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent is removed under reduced pressure and the solids are dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains a white solid. Recrystallization from hot ethyl acetate and hexane will afford N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane.

Alternate General Procedure for the Synthesis of Amino EpoxidesStep A:

20

A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) is heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) is then slowly added (addition time ~25 min). The mixture is then stirred at 97°C for 30 minutes. The solution is cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers are then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product is then used in the next step without purification.

30

Step B:

The crude benzylated product of the above step is dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) is then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture is stirred for 20 minutes at -55°C. The reaction is quenched at -55°C by the slow addition of methanol (37 ml). The cold solution is then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) is filtered off and washed with toluene. The solid material is suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture is cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid is dissolved. The toluene layer is separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) are then added to the residue upon which the alcohol product begins to crystallize. After 30 min., an additional 50 ml hexane is added to promote further crystallization. The solid is filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material can be isolated by refiltering the mother liquor. The solids are combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors are combined and concentrated (34 g). The residue is created with ethyl acetate and hexane which provides an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) is cooled to -74°C. A

solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) is then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture is stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution is stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) is then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture is stirred for 30 min. and then water (225 ml) is added. The dichloromethane layer is separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue is diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate is concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

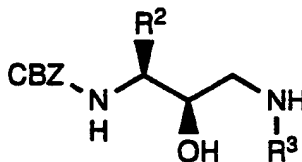
Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

A solution of the crude aldehyde 0.074 mol and chloriodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) is cooled to -78°C. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) is then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloriodomethane (1.6 ml, 0.022 mol) is added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture is stirred for 15 min. Each of the reagents, chloriodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) are added 4 more times over 45 min. at -75°C. The cooling bath is then removed and the solution warmed to 22°C over 1.5 hr. The mixture is poured into 300 ml of saturated aq.

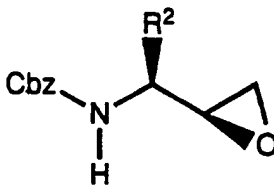
ammonium chloride solution. The tetrahydrofuran layer is separated. The aqueous phase is extracted with ethyl acetate (1 x 300 ml). The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at the subsequent sulfonamide formation step.

Alternately, the product could be purified by chromatography.

General Procedure for the Synthesis of 1,3-Diamino 4-phenyl Butan-2-ol Derivatives:



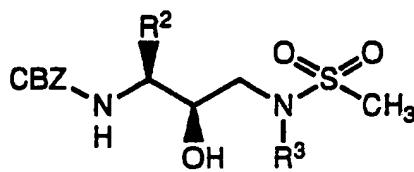
A mixture of the amine R³NH₂ (20 equiv.) in dry isopropyl alcohol (20mL/mmol of epoxide to be converted) is heated to reflux and then is treated with an N-Cbz amino epoxide of the formula:



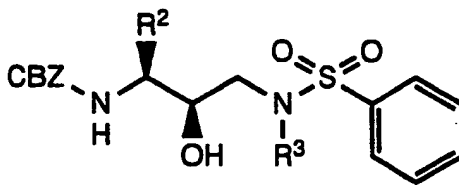
from a solids addition funnel over a 10-15 minute period. After the addition is complete the solution is maintained at reflux for an additional 15 minutes and the progress of the reaction monitored by TLC. The reaction mixture is then concentrated in vacuo to give an oil and is then treated with n-hexane with rapid stirring whereupon the ring opened-material precipitates from solution.

Precipitation is generally complete within 1 hr and the product is then isolated by filtration on a Büchner funnel and is then air dried. The product is further dried in vacuo. This method affords amino alcohols of sufficient purity for most purposes.

General procedure for the Reaction of Amino Alcohols with Sulfonyl Halides or Sulfonyl Anhydrides: Preparation of Sulfonamides



To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2 mmol) and triethylamine (723 uL, 5.5 mmol) in dichloromethane (20 mL) is added dropwise methanesulfonyl chloride (400 uL, 5.2 mmol). The reaction mixture is stirred for 2 hours at room temperature, then the dichloromethane solution is concentrated to ca. 5 mL and applied to a silica gel column (100 gm). The column is eluted with chloroform containing 1% ethanol and 1% methanol.



25

Alternatively, from the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one can obtain the appropriate (phenylsulfonyl)amino derivative.

General Procedure for the Removal of the Protecting
Groups by Hydrogenolysis with Palladium on Carbon

A. Alcohol Solvent

5 The Cbz-protected peptide derivative is
dissolved in methanol (ca.20mL/mmol) and 10% palladium on
carbon catalyst is added under a nitrogen atmosphere.
The reaction vessel is sealed and flushed 5 times with
nitrogen and then 5 times with hydrogen. The pressure is
10 maintained at 50 psig for 1-16 hours and then the
hydrogen is replaced with nitrogen and the solution is
filtered through a pad of celite to remove the catalyst.
The solvent is removed in vacuo to give the free amino
derivative of suitable purity to be taken directly on to
15 the next step.

B. Acetic Acid Solvent

 The Cbz-protected peptide derivative is
dissolved in glacial acetic acid (20mL/mmol) and 10%
20 palladium on carbon catalyst is added under a nitrogen
atmosphere. The reaction vessel is flushed 5 times with
nitrogen and 5 times with hydrogen and then maintained at
40 psig for about 2h. The hydrogen is then replaced with
nitrogen and the reaction mixture filtered through a pad
25 of celite to remove the catalyst. The filtrate is
concentrated and the resulting product is taken up in
anhydrous ether and is evaporated to dryness 3 times.
The final product, the acetate salt, is dried in vacuo
and is of suitable purity for subsequent conversion.

30

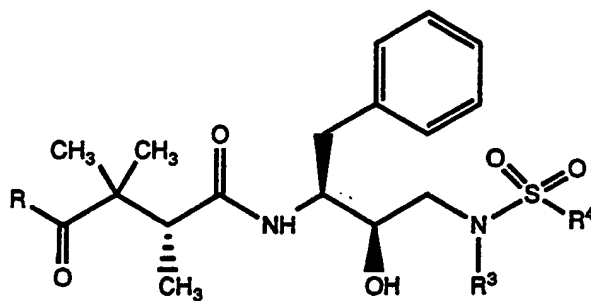
General Procedure for Removal of Boc-protecting Group
with 4N Hydrochloric Acid in Dioxane

 The Boc-protected amino acid or peptide is
35 treated with a solution of 4N HCl in dioxane with

stirring at room temperature. Generally the deprotection reaction is complete within 15 minutes, the progress of the reaction is monitored by thin layer chromatography (TLC). Upon completion, the excess dioxane and HCl are removed by evaporation in vacuo. The last traces of dioxane and HCl are best removed by evaporation again from anhydrous ether or acetone. The hydrochloride salt thus obtained is thoroughly dried in vacuo and is suitable for further reaction.

TABLE 2

5



| | Entry | R | R ³ | R ⁴ |
|----|-------|-----------------|-------------------------------|--|
| 10 | 1 | OH | CH ₃ | C ₆ H ₅ |
| | 2 | OH | i-Butyl | CH ₃ |
| | 3 | OH | i-Butyl | n-Butyl |
| | 4 | NH ₂ | i-Butyl | n-Butyl |
| | 5 | OH | i-Propyl | n-Butyl |
| 15 | 6 | NH ₂ | i-Propyl | n-Butyl |
| | 7 | OH | C ₆ H ₅ | n-Butyl |
| | 8 | OH | -CH ₂ - | n-Butyl |
| | 9 | OH | -CH ₂ - | n-Butyl |
| | 10 | NH ₂ | -CH ₂ - | n-Butyl |
| 20 | 11 | OH | | n-Butyl |
| | 12 | OH | i-Butyl | n-Propyl |
| | 13 | OH | i-Butyl | -CH ₂ CH(CH ₃) ₂ |
| | 14 | OH | (R)-CH(CH ₃)- | n-Butyl |
| | 15 | OH | -CH ₂ - | i-Propyl |

TABLE 2 (Cont'd)









| | Entry | R | R ³ | R ⁴ |
|----|-------|-----------------|--|---|
| 5 | 16 | OH | $-\text{CH}_2-$  | $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ |
| | 17 | OH | i-Butyl | $-\text{CH}_2\text{CH}_3$ |
| | 18 | OH | i-Butyl | $-\text{CH}(\text{CH}_3)_2$ |
| | 19 | OH | i-Butyl |  |
| | 20 | NH ₂ | i-Butyl |  |
| 10 | 21 | OH | $-\text{CH}_2-$  | $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$ |
| | 22 | OH | $(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$ | $-\text{CH}(\text{CH}_3)_2$ |
| | 23 | NH ₂ | i-Butyl | $-\text{CH}(\text{CH}_3)_2$ |
| | 24 | OH | i-Butyl | $-\text{C}(\text{CH}_3)_3$ |
| | 25 | NH ₂ | i-Butyl | $-\text{C}(\text{CH}_3)_3$ |
| 15 | 26 | OH | $-\text{CH}_2-$  | $-\text{C}(\text{CH}_3)_3$ |
| | 27 | NH ₂ | $-\text{CH}_2-$  | $-\text{C}(\text{CH}_3)_3$ |
| | 28 | OH | $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$ | $-\text{C}(\text{CH}_3)_3$ |
| | 29 | NH ₂ | $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$ | $-\text{C}(\text{CH}_3)_3$ |
| | 30 | OH | $-\text{CH}_2\text{C}_6\text{H}_5$ | $-\text{C}(\text{CH}_3)_3$ |
| 20 | 31 | NH ₂ | $-\text{CH}_2\text{C}_6\text{H}_5$ | $-\text{C}(\text{CH}_3)_3$ |
| | 32 | OH | $-(\text{CH}_2)_2\text{C}_6\text{H}_5$ | $-\text{C}(\text{CH}_3)_3$ |
| | 33 | NH ₂ | $-(\text{CH}_2)_2\text{C}_6\text{H}_5$ | $-\text{C}(\text{CH}_3)_3$ |
| | 34 | OH | n-Butyl | $-\text{C}(\text{CH}_3)_3$ |
| | 35 | OH | n-Pentyl | $-\text{C}(\text{CH}_3)_3$ |
| 25 | 36 | OH | n-Hexyl | $-\text{C}(\text{CH}_3)_3$ |
| | 37 | OH | $-\text{CH}_2-$  | $-\text{C}(\text{CH}_3)_3$ |
| | 38 | OH | $-\text{CH}_2\text{C}(\text{CH}_3)_3$ | $-\text{C}(\text{CH}_3)_3$ |
| | 39 | NH ₂ | $-\text{CH}_2\text{C}(\text{CH}_3)_3$ | $-\text{C}(\text{CH}_3)_3$ |
| | 40 | OH | $-\text{CH}_2\text{CH}_2-\text{N}$  | $-\text{C}(\text{CH}_3)_3$ |
| 30 | 41 | OH | $-\text{CH}_2\text{C}_6\text{H}_5\text{OCH}_3$ (para) | $-\text{C}(\text{CH}_3)_3$ |

TABLE 2 (Cont'd)

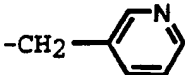
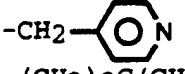

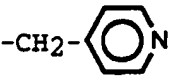



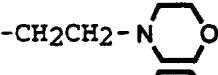
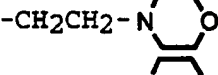
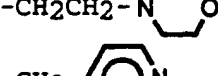
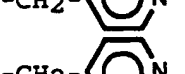
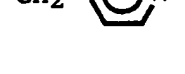
| | Entry | R | R ³ | R ⁴ |
|----|-------|---------------------|--|-----------------------------------|
| 5 | | | | |
| | 42 | OH |  | -C(CH ₃) ₃ |
| | 43 | OH |  | -C(CH ₃) ₃ |
| | 44 | OH | -(CH ₂) ₂ C(CH ₃) ₃ | -C(CH ₃) ₃ |
| | 45 | NH ₂ | -(CH ₂) ₂ C(CH ₃) ₃ | -C(CH ₃) ₃ |
| 10 | 46 | OH | -(CH ₂) ₄ OH | -C(CH ₃) ₃ |
| | 47 | NH ₂ | -(CH ₂) ₄ OH | -C(CH ₃) ₃ |
| | 48 | NH ₂ |  | -C(CH ₃) ₃ |
| | 49 | NH ₂ |  | -C(CH ₃) ₃ |
| | 50 | OCH ₂ Ph |  | -C ₆ H ₅ |
| 15 | 51 | OH |  | -C ₆ H ₅ |
| | 52 | NH ₂ |  | -C ₆ H ₅ |
| | 53 | OCH ₂ Ph | -CH ₂ C ₆ H ₁₁ | -C ₆ H ₅ |
| | 54 | OH | -CH ₂ C ₆ H ₁₁ | -C ₆ H ₅ |
| | 55 | NH ₂ | -CH ₂ C ₆ H ₁₁ | -C ₆ H ₅ |
| 20 | 56 | OCH ₂ Ph | -CH ₂ Ph | -C ₆ H ₅ |
| | 57 | OH | -CH ₂ Ph | -C ₆ H ₅ |
| | 58 | NH ₂ | -CH ₂ Ph | -C ₆ H ₅ |
| | 59 | OCH ₂ Ph |  | -C ₆ H ₅ |
| | 60 | OH |  | -C ₆ H ₅ |
| 25 | 61 | NH ₂ |  | -C ₆ H ₅ |
| | 62 | OCH ₂ Ph |  | -C ₆ H ₅ |
| | 63 | OH |  | -C ₆ H ₅ |

TABLE 2 (Cont'd)














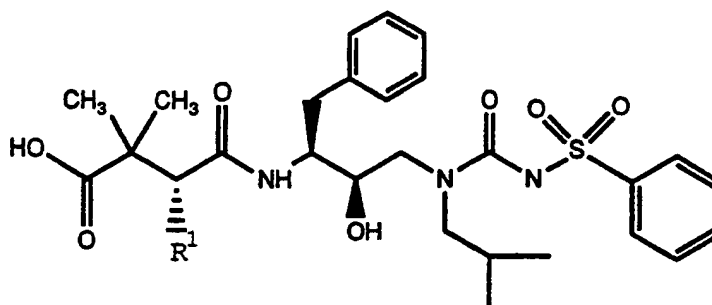
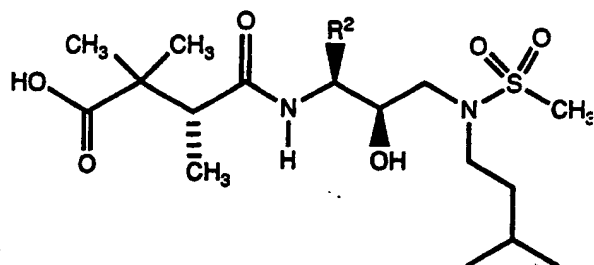
| | Entry | R | R ³ | R ⁴ |
|----|-------|---------------------|---|---|
| 5 | 64 | NH ₂ | -CH ₂ -  | -C ₆ H ₅ |
| | 65 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -CH ₃ |
| | 66 | OH | -CH ₂ CH(CH ₃) ₂ | -CH ₃ |
| | 67 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -CH ₃ |
| | 68 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -C ₆ H ₁₁ |
| 10 | 69 | OH | -CH ₂ CH(CH ₃) ₂ | -C ₆ H ₁₁ |
| | 70 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -C ₆ H ₁₁ |
| | 71 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ |  |
| | 72 | OH | -CH ₂ CH(CH ₃) ₂ |  |
| | 73 | NH ₂ | -CH ₂ CH(CH ₃) ₂ |  |
| 15 | 74 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -CF ₃ |
| | 75 | OH | -CH ₂ CH(CH ₃) ₂ | -CF ₃ |
| | 76 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -CF ₃ |
| | 77 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -  -OCH ₃ |
| | 78 | OH | -CH ₂ CH(CH ₃) ₂ | -  -OCH ₃ |
| 20 | 79 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -  -OCH ₃ |
| | 80 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -  -F |
| | 81 | OH | -CH ₂ CH(CH ₃) ₂ | -  -F |
| | 82 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -  -F |
| | 83 | OCH ₂ Ph | -CH ₂ CH(CH ₃) ₂ | -  -NH ₂ |
| 25 | 84 | OH | -CH ₂ CH(CH ₃) ₂ | -  -NH ₂ |
| | 85 | NH ₂ | -CH ₂ CH(CH ₃) ₂ | -  -NH ₂ |

TABLE 3



5

| Entry | R ¹ |
|-------|---|
| 1 | CH ₂ SO ₂ CH ₃ |
| 10 | (R) -CH(OH)CH ₃ |
| 3 | CH(CH ₃) ₂ |
| 4 | (R, S)CH ₂ SOCH ₃ |
| 5 | CH ₂ SO ₂ NH ₂ |
| 6 | CH ₂ SCH ₃ |
| 15 | 7 CH ₂ CH(CH ₃) ₂ |
| 8 | CH ₂ CH ₂ C(O)NH ₂ |
| 9 | (S) -CH(OH)CH ₃ |
| 10 | -CH ₂ C(CH ₃) ₂ |
| 11 | -CH ₂ CH ₃ |
| 20 | 12 -CH ₂ C(O)NH ₂ |

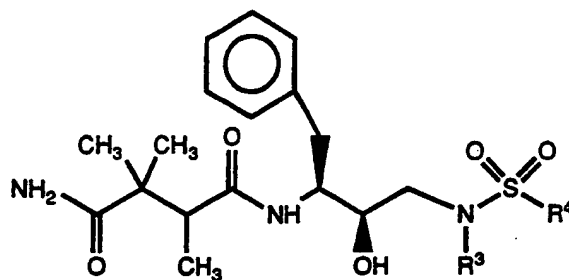
TABLE 4

5

| Entry | | R ² |
|-------|---|---|
| 10 | 1 | n-Bu |
| | 2 | cyclohexylmethyl |
| | 3 | C ₆ H ₅ CH ₂ |
| | 4 | 2-naphthylmethyl |
| | 5 | p-F (C ₆ H ₄)CH ₂ |
| | 6 | p-(PhCH ₂ O) (C ₆ H ₄)CH ₂ |
| | 7 | p-HO (C ₆ H ₄)CH ₂ |

15

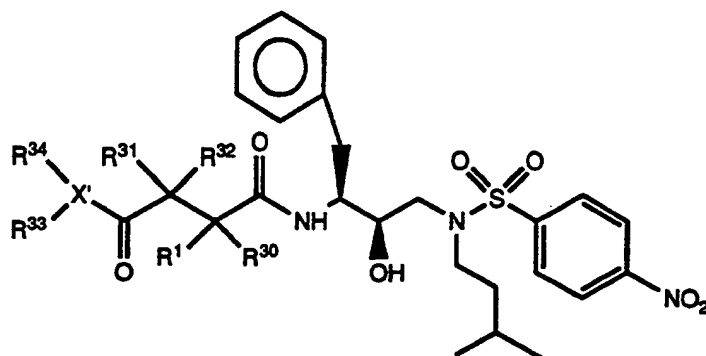
TABLE 5



5

| Entry | R ³ | R ⁴ |
|-------|--|--|
| 1 | -CH ₂ CH(CH ₃) ₂ | -CH(CH ₃) ₂ |
| 10 | 2 | -CH ₂ CH(CH ₃) ₂ |
| 3 | -CH ₂ CH(CH ₃) ₂ | |
| 4 | -CH ₂ CH(CH ₃) ₂ | |
| 5 | -CH ₂ CH(CH ₃) ₂ | |
| 5 | -CH ₂ CH(CH ₃) ₂ | |

TABLE 6



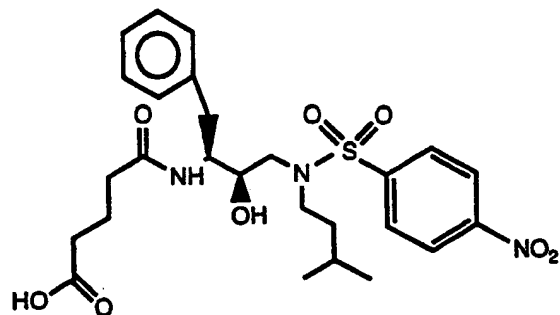
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| Entry | R1 | R30 | R31 | R32 | X' | R33 | R34 |
|-------|----|-----------------|-----------------|-----------------|----|---|-----------------|
| 10 | 1 | H | H | H | N | H | H |
| | 2 | H | H | H | O | H | - |
| | 3 | H | H | H | O | CH ₃ | - |
| | 4 | CH ₃ | H | H | N | H | H |
| | 5 | CH ₃ | H | H | O | H | - |
| 15 | 6 | H | H | CH ₃ | N | H | H |
| | 7 | H | H | CH ₃ | O | H | - |
| | 8 | CH ₃ | CH ₃ | H | N | H | H |
| | 9 | CH ₃ | CH ₃ | H | O | H | - |
| | 10 | CH ₃ | CH ₃ | H | O | CH ₂ C ₆ H ₄ OCH ₃ | - |
| 20 | 11 | H | H | CH ₃ | N | H | H |
| | 12 | H | H | CH ₃ | O | H | - |
| | 13 | H | H | CH ₃ | O | CH ₂ C ₆ H ₄ OCH ₃ | - |
| | 14 | CH ₃ | H | CH ₃ | N | H | H |
| | 15 | CH ₃ | H | CH ₃ | N | H | CH ₃ |
| 25 | 16 | CH ₃ | H | CH ₃ | N | CH ₃ | CH ₃ |
| | 17 | CH ₃ | H | CH ₃ | O | H | - |
| | 18 | CH ₃ | H | CH ₃ | O | -CH ₂ C ₆ H ₅ OCH ₃ | - |
| | 19 | OH | H | H | N | H | H |
| | 20 | OH | H | H | O | H | - |
| 30 | 21 | H | H | OH | N | H | H |
| | 22 | H | H | OH | O | H | - |

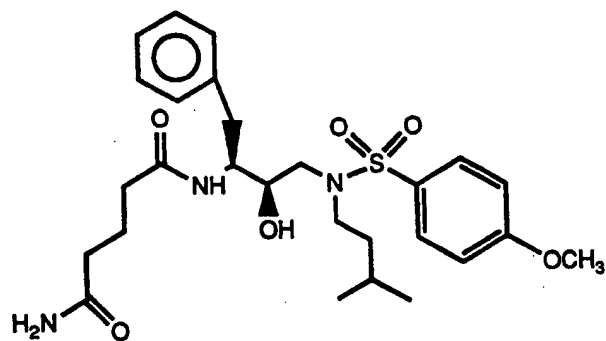
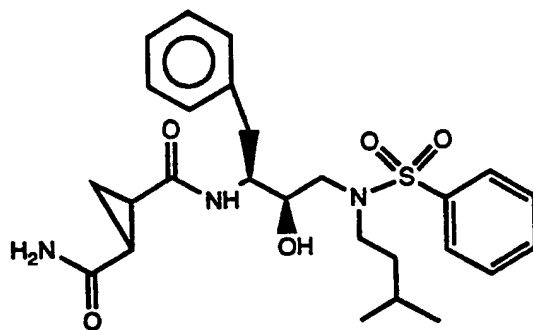
TABLE 6 (Cont'd.)

| | Entry | R ¹ | R ³⁰ | R ³¹ | R ³² | X' | R ³³ | R ³⁴ |
|----|-------|-------------------------------------|-----------------|---------------------------------|---------------------------------|----|--------------------|-----------------|
| 5 | 23 | CH ₂ | H | H | H | N | H | H |
| | 24 | CH ₂ C(O)NH ₂ | H | H | H | N | H | H |
| | 25 | CH ₂ C(O)NH ₂ | H | H | H | O | H | - |
| | 26 | CH ₂ C(O)NH ₂ | H | H | H | O | CH ₃ | - |
| 10 | 27 | CH ₂ Ph | H | H | H | N | H | H |
| | 28 | CH ₃ | H | CH ₃ | CH ₃ | O | CH ₂ Ph | - |
| | 29 | CH ₃ | H | CH ₃ | CH ₃ | O | H | - |
| | 30 | CH ₃ | H | CH ₃ | CH ₃ | N | H | H |
| | 31 | CH ₃ | H | CH ₃ | CH ₃ | N | H | CH ₃ |
| 15 | 32 | CH ₃ | H | CH ₃ | CH ₃ | N | CH ₃ | CH ₃ |
| | 33 | CH ₂ CH ₃ | H | CH ₃ | CH ₃ | O | H | - |
| | 34 | CH ₂ CH ₃ | H | CH ₃ | CH ₃ | N | H | H |
| | 35 | CH ₃ | H | CH ₂ CH ₃ | CH ₂ CH ₃ | O | H | - |
| | 36 | CH ₃ | H | CH ₂ CH ₃ | CH ₂ CH ₃ | N | H | H |
| 20 | | | | | | | | |

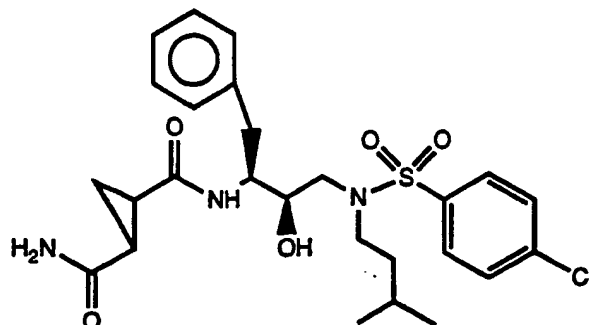
TABLE 7



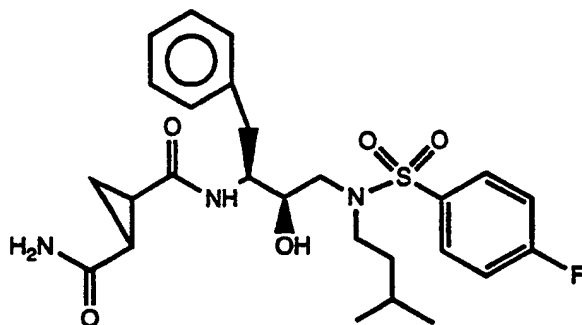
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10

TABLE 7 (Cont'd.)

5



10

Example 9

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC₅₀ (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 8. The enzyme method is described below. The substrate is 2-aminobenzoyl-Ile-Nle-Phe(p-NO₂)-Gln-ArgNH₂. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)) The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4
20% glycerol
1 mM EDTA
1 mM DTT
0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μ M.

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10 μ l of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40 μ l of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

TABLE 8

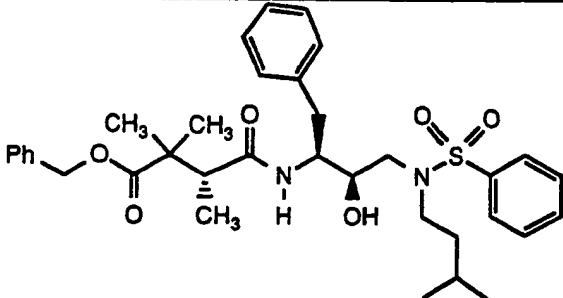
| Entry | Compound | IC ₅₀ (nM) |
|-------|--|-----------------------|
| 1 |  | 80 |

TABLE 8
(continued)

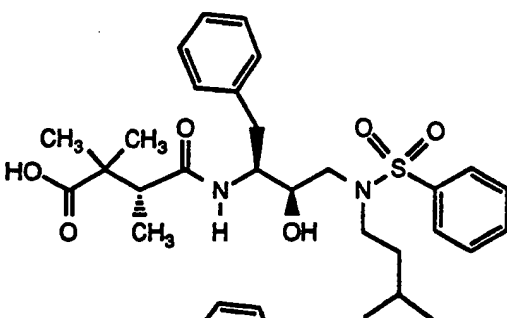
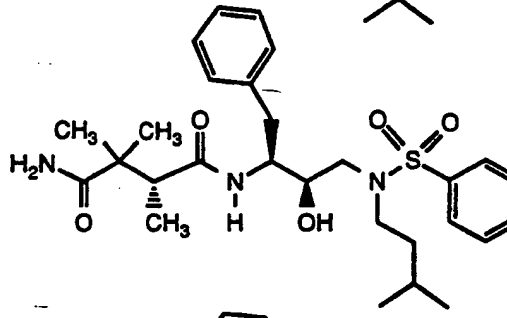
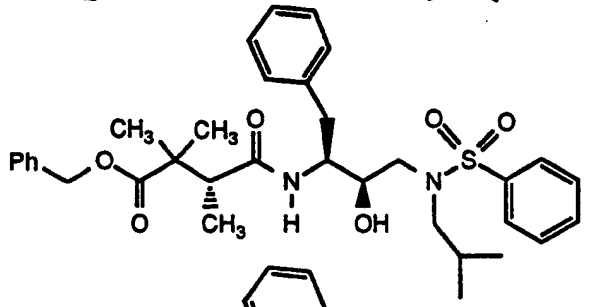
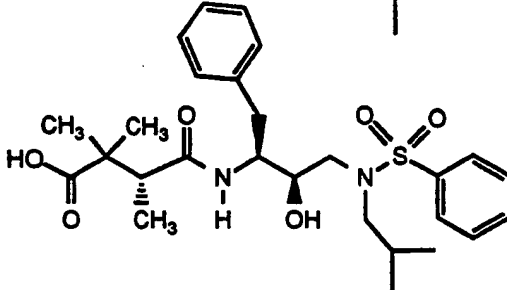
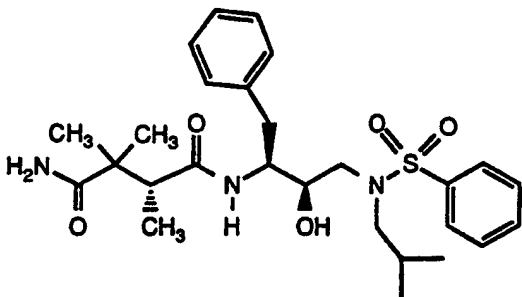
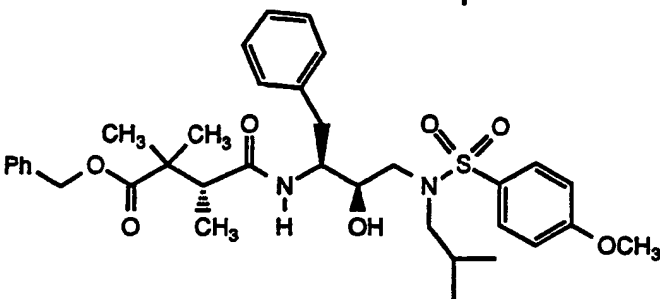
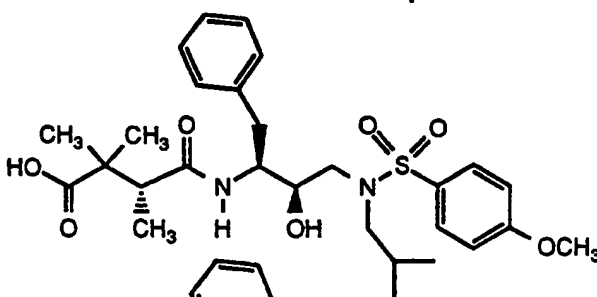
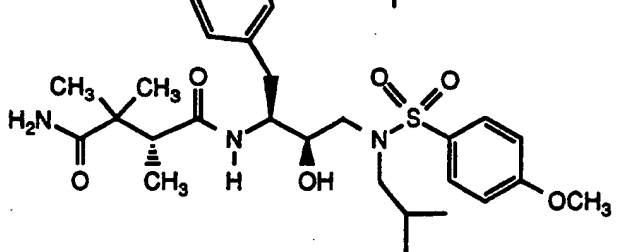
| Entry | Compound | IC ₅₀ (nM) |
|-------|--|-----------------------|
| 2 |  | 2 |
| 3 |  | 2 |
| 4 |  | 34 |
| 5 |  | 1 |

TABLE 8
(continued)

| Entry | Compound | IC ₅₀ (nM) |
|-------|--|-----------------------|
| 6 |  | 2 |
| 7 |  | 16 |
| 8 |  | 2 |
| 9 |  | 2 |

Example 10

The effectiveness of the compounds listed in Table 8 were determined in the above-described enzyme

assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pawles et al, J. Virol. Methods 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4+ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2µg/ml). An 80 µl volume of medium containing 1×10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100µl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5×10^4 TCID₅₀ per ml (TCID₅₀ = the dose of virus that infects 50% of cells in tissue culture), and a 20µL volume of the virus sample (containing 1000 TCID₅₀ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

30

| | Cells | Drug | Virus |
|----|-------|------|-------|
| 35 | | | |
| 1. | + | - | - |
| 2. | + | + | - |
| 3. | + | - | + |
| 4. | + | + | + |

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 µg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

10

Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO₂ atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100µl sample of each cell suspension was removed for assay. A 20µL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100µL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO₂ environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100µl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

30

TABLE 9

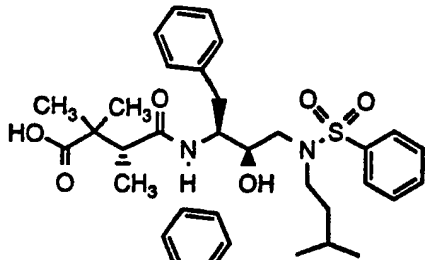
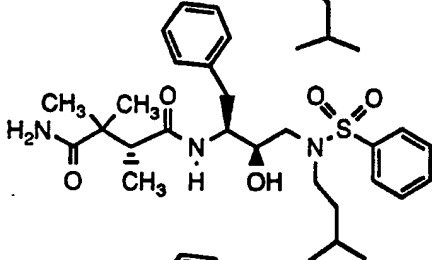
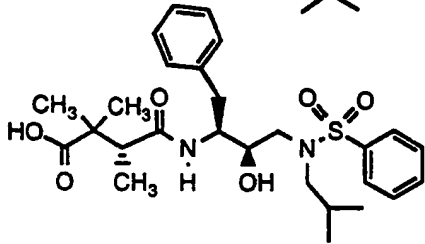
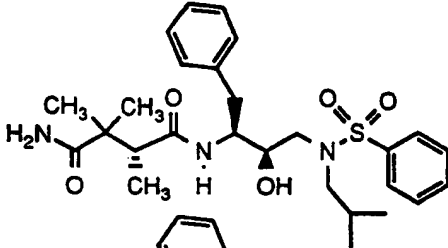
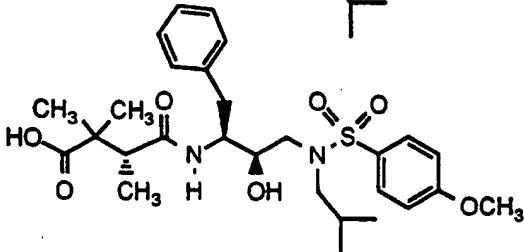
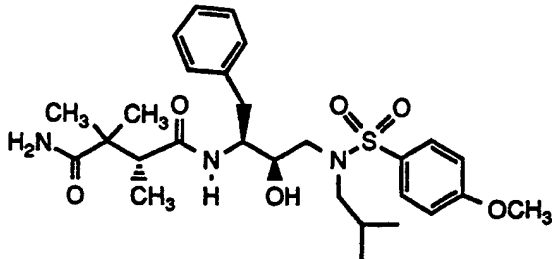
| Entry | Compound | IC ₅₀ (nm) | EC ₅₀ (nm) | TD ₅₀ (nm) |
|-------|---|-----------------------|-----------------------|-----------------------|
| 1 |  | 2 | 15 | |
| 2 |  | 2 | 9 | 60,000 |
| 3 |  | 1 | 42 | 220,000 |
| 4 |  | 2 | 5 | 62,000 |
| 5 |  | 2 | 27 | 200,000 |

TABLE 9
(continued)

| 5 | Entry | Compound | IC ₅₀ (nm) | EC ₅₀ (nm) | TD ₅₀ (nm) |
|---|-------|---|-----------------------|-----------------------|-----------------------|
| 6 | |  | 2 | 5 | 58,000 |

10 Utilizing the procedures set forth above in the
examples along with the general description, it is
contemplated that the compounds listed below could be
prepared and that such compounds would have activities as
HIV protease inhibitors substantially similar to the
15 activities of the compounds set forth in the examples.

The compounds of the present invention are
effective antiviral compounds and, in particular, are
effective retroviral inhibitors as shown above. Thus,
20 the subject compounds are effective HIV protease
inhibitors. It is contemplated that the subject
compounds will also inhibit other strains of HIV such as
HIV-2, and other viruses such as human T-cell leukemia
virus, simian immunodeficiency virus, feline leukemia
25 virus, respiratory syncytial virus, hepadnavirus,
cytomegalovirus and picornavirus. Thus, the subject
compounds are effective in the treatment and/or
prophylaxis of retroviral infections.

30 Compounds of the present can possess one or more
asymmetric carbon atoms and are thus capable of existing in
the form of optical isomers as well as in the form of

racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with
5 an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically
10 active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric
15 molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then
20 hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

25

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate,
30 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride,
35 hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate,

propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological

considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part
5 of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be
10 administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of
15 transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

20
Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The
25 sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water,
30 Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty
35 acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the

drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and
5 will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be
10 admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as
15 magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may
20 include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and
25 sweetening, flavoring, and perfuming agents.

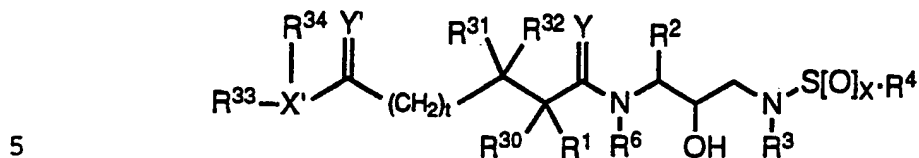
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more
30 immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT or with N-butyl-1-deoxynojirimycin for the prophylaxis and/or treatment of AIDS. When administered as a combination, the
35 therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which
5 are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in
10 the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

10 x represents 0, 1 or 2;

t represents either 0 or 1;

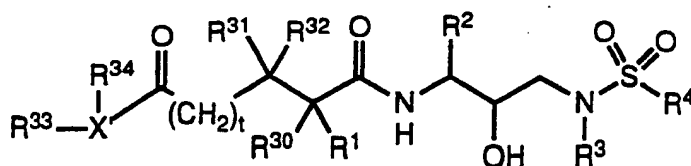
15 R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃,
-CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂,
-C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S(O)CH₃),
-C(CH₃)₂(S(O)₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and
20 cycloalkyl radicals and amino acid side chains selected
from asparagine, S-methyl cysteine and the corresponding
sulfoxide and sulfone derivatives thereof, glycine,
leucine, isoleucine, allo-isoleucine, tert-leucine,
phenylalanine, ornithine, alanine, histidine, norleucine,
glutamine, valine, threonine, serine, o-alkyl serine,
aspartic acid, beta-cyano alanine, and allothreonine side
25 chains;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and
aralkyl radicals, which radicals are optionally
substituted with a group selected from halogen and alkyl
30 radicals, -NO₂, -C≡N, CF₃, -OR⁹ and -SR⁹, wherein R⁹
represents hydrogen and alkyl radicals;

R³ represents hydrogen, alkyl, haloalkyl, alkenyl,
alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl,
35 cycloalkylalkyl, heterocycloalkyl, heteroaryl,

- heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;
- X' represents N, O, and C(R¹⁷) wherein R¹⁷ represents hydrogen and alkyl radicals;
- Y and Y' independently represent O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³;
- R⁴ represents radicals as defined by R³ except for hydrogen;
- R⁶ represents hydrogen and alkyl radicals;
- R³⁰, R³¹ and R³² represent radicals as defined for R¹, or one of R¹ and R³⁰ together with one of R³¹ and R³² and the carbon atoms to which they are attached form a cycloalkyl radical; or R³⁰ and R³² together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical; and
- R³³ and R³⁴ independently represent hydrogen, radicals as defined for R³, or R³³ and R³⁴ together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R³⁴ is absent.

2. Compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

5

t represents either 0 or 1;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃,
 -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂,
 10 -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃),
 -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and
 cycloalkyl radicals and amino acid side chains selected
 from asparagine, S-methyl cysteine and the corresponding
 sulfoxide and sulfone derivatives thereof, glycine,
 15 leucine, isoleucine, allo-isoleucine, tert-leucine,
 phenylalanine, ornithine, alanine, histidine, norleucine,
 glutamine, valine, threonine, serine, aspartic acid, beta-
 cyano alanine, and allothreonine side chains;

20 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and
 aralkyl radicals, which radicals are optionally
 substituted with a group selected from alkyl and halogen
 radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹
 represents hydrogen and alkyl radicals;

25

R³ represents hydrogen, alkyl, haloalkyl, alkenyl,
 alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl,
 cycloalkylalkyl, heterocycloalkyl, heteroaryl,
 heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl,
 30 aminoalkyl and mono- and disubstituted aminoalkyl
 radicals, wherein said substituents are selected from
 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,
 heteroaryl, heteroaralkyl, heterocycloalkyl, and
 heterocycloalkylalkyl radicals, or in the case of a

disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

- 5 X' represents N, O, and C(R¹⁷) wherein R¹⁷ represents hydrogen and alkyl radicals;

R⁴ represents radicals as defined by R³ except for hydrogen;

10

- R³⁰, R³¹ and R³² represent radicals as defined for R¹, or one of R¹ and R³⁰ together with one of R³¹ and R³² and the carbon atoms to which they are attached form a cycloalkyl radical; or R³¹ and R³² together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical; and

- 15 R³³ and R³⁴ independently represent hydrogen and radicals as defined for R³, or R³³ and R³⁴ together with X' represent cycloalkyl, aryl, heterocyclyl and heteroaryl radicals, provided that when X' is O, R³⁴ is absent.

- 25 3. Compound of Claim 2 wherein t is O and X' is O.

25

4. Compound of Claim 2 wherein t is O.

5. Compound of Claim 2 wherein X' represents N and O.

30

6. Compound of Claim 2 wherein t is 1.

7. Compound of Claim 2 wherein R¹ represents hydrogen, alkyl, alkenyl, alkynyl, aralkyl, and hydroxyl radicals, and radicals selected from -(CH₂)C(O)CH₃, -CH₂SO₂NH₂, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S(O)CH₃) and -C(CH₃)₂(S(O)₂CH₃).

35

8. Compound of Claim 2 wherein R¹ represents hydrogen, methyl, ethyl, propargyl, t-butyl, isopropyl, sec-butyl, benzyl and phenylpropyl radicals;
- 5
9. Compound of Claim 2 wherein R¹ represents a methyl radical.
- 10
10. Compound of Claim 2 wherein R¹ represents an alkyl radical when t is 0.
11. Compound of Claim 2 wherein R¹ and R³¹ are both hydrogen and R³⁰ and R³² are both methyl.
- 15
12. Compound of Claim 2 wherein R¹, R³¹ and R³² are methyl and R³⁰ is hydrogen.
13. Compound of Claim 2 wherein R¹ is methyl and R³⁰, R³¹ and R³² are hydrogen.
- 20
14. Compound of Claim 2 wherein R³⁰ is hydrogen and R¹, R³¹ and R³² are methyl.
15. Compound of Claim 2 wherein R¹ and R³¹ are hydrogen and R³⁰ and R³² together with the carbon atoms to which they are attached form a three- to six-membered cycloalkyl radical.
- 25
16. Compound of Claim 2 wherein t is 0 and X' is N.
- 30
17. Compound of Claim 2 wherein t is 1 and X' is N.
18. Compound of Claim 2 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹
- 35

wherein R⁹ represents alkyl radicals.

19. Compound of Claim 2 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals.

5

20. Compound of Claim 2 wherein R² represents aralkyl radicals.

21. Compound of Claim 2 wherein R² represents
10 CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

22. Compound of Claim 2 wherein R² represents an n-butyl and iso-butyl radicals.

15

23. Compound of Claim 2 wherein R² represents benzyl, 4-fluorobenzyl and 2-naphthylmethyl radicals.

24. Compound of Claim 2 wherein R² represents
20 a cyclohexylmethyl radical.

25. Compound of Claim 2 wherein R³ and R⁴ independently represent alkyl, alkenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl,
25 heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, aryl, aralkyl and heteroaralkyl radicals.

26. Compound of Claim 2 wherein R⁴ represents an aryl radical.

30

27. Compound of Claim 2 wherein R³ and R⁴ independently represent alkyl and aryl radicals.

28. Compound of Claim 2 wherein R³ and R⁴
35 independently represent alkyl and hydroxyalkyl radicals.

29. Compound of Claim 2 wherein R³ and R⁴ independently represent alkyl, cycloalkyl and

cycloalkylalkyl radicals.

30. Compound of Claim 2 wherein R³ and R⁴
independently represent alkyl, heterocycloalkyl and
5 heterocycloalkylalkyl radicals.

31. Compound of Claim 2 wherein R³ and R⁴
independently represent alkyl, aryl and aralkyl radicals.

10 32. Compound of Claim 2 wherein R⁴ represents
alkyl and aryl radicals.

33. Compound of Claim 2 wherein R³ represents
alkyl radicals having from about 2 to about 5 carbon
15 atoms.

34. Compound of Claim 2 wherein R³ represents
n-pentyl, n-hexyl, n-propyl, i-butyl, neo-pentyl, i-amyl,
and n-butyl radicals.
20

35. Compound of Claim 2 wherein R³ and R⁴
independently represent alkyl radicals having from about
2 to about 5 carbon atoms, cycloalkylalkyl radicals, aryl
radicals, aralkyl radicals, heterocycloalkylalkyl
25 radicals, heteroaryl radicals and heteroaralkyl radicals.

36. Compound of Claim 2 wherein R³ represents
benzyl, para-fluorobenzyl, para-methoxybenzyl, para-
methylbenzyl, and 2-naphthylmethyl radicals and R⁴
30 represents phenyl.

37. Compound of Claim 2 wherein R³ is
cyclohexylmethyl or cyclohexyl and R⁴ is phenyl or
methyl.
35

38. Compound of Claim 2 wherein R³ is i-amyl
and R⁴ is phenyl or methyl.

39. Compound of Claim 2 wherein R³ is i-butyl and R⁴ is phenyl or methyl.

40. Compound of Claim 2 wherein R³ is n-butyl and R⁴ is phenyl or methyl.

41. Compound of Claim 2 wherein R³ is neopentyl and R⁴ is phenyl or methyl.

42. Compound of Claim 2 wherein R⁴ represents alkyl and cycloalkyl radicals.

43. Compound of Claim 2 wherein R⁴ represents aryl and heteroaryl radicals.

44. Compound of Claim 2 wherein R⁴ represents alkyl radicals.

45. Compound of Claim 2 wherein R³ represents heteroaralkyl radicals and R⁴ is an aryl or alkyl radical.

46. Compound of Claim 2 wherein R³ is a p-fluorobenzyl radical and R⁴ is a phenyl radical.

47. Compound of Claim 2 wherein R³ is a 4-pyridylmethyl radical or its N-oxide and R⁴ is a phenyl radical.

48. Compound of Claim 2 wherein R⁴ is selected from methyl, phenyl, p-methoxyphenyl, p-fluorophenyl, p-aminophenyl and p-(acetylamino)phenyl.

49. Compound of Claim 2 wherein R³ represents isobutyl, isoamyl, n-propyl, cyclohexyl, cyclohexylmethyl and n-butyl radicals and R⁴ represents phenyl radicals and substituted phenyl radicals, wherein substituents of

the substituted phenyl radical are selected from chloro, fluoro, nitro, methoxy, and amino substituents.

50. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent hydrogen and alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.
51. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent hydrogen and alkyl radicals.
52. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent alkenyl and alkynyl radicals
53. Compound of Claim 2 wherein X' is nitrogen R³³ and R³⁴ independently represent hydroxyalkyl and alkoxyalkyl radicals.
54. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent alkyl radicals.
55. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent cycloalkyl and cycloalkylalkyl radicals.
56. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent heteroaryl and heteroaralkyl radicals.
57. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ independently represent heterocycloalkyl radicals.

58. Compound of Claim 2 wherein X' is nitrogen and R³³ and R³⁴ together with the nitrogen atom form a heterocyclyl or heteroaryl radical.

5 59. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ represents hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals.

10

60. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ represents alkyl, aralkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroaralkyl radicals.

15

61. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ is an aralkyl radical.

20 62. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ is hydrogen.

63. Compound of Claim 2 wherein t is 0 and R¹, R³⁰ and R³¹ are all hydrogen.

25 64. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ is an alkyl radical.

30 65. Compound of Claim 2 wherein X' is oxygen, R³⁴ is absent and R³³ is a benzyl radical.

66. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

35 67. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

68. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 66.

5 69. Method of Claim 68 wherein the retroviral protease is HIV protease.

70. Method of treating a retroviral infection comprising administering an effective amount of a
10 composition of Claim 66.

71. Method of Claim 70 wherein the retroviral infection is an HIV infection.

15 72. Method for treating AIDS comprising administering an effective amount of a composition of Claim 66.

73. Method of inhibiting a retroviral protease
20 comprising administering a protease inhibiting amount of a composition of Claim 67.

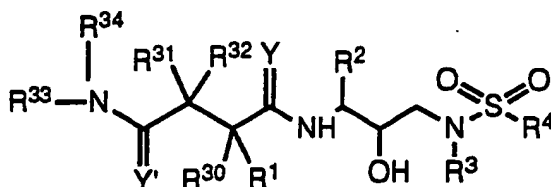
74. Method of Claim 73 wherein the retroviral protease is HIV protease.
25

75. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 67.

30 76. Method of Claim 75 wherein the retroviral infection is an HIV infection.

77. Method for treating AIDS comprising administering an effective amount of a composition of
35 Claim 67.

78. Compound represented by the formula:



- 5 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein:
- R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂,
 10 -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine,
 15 leucine, isoleucine, allo-isoleucine, tert-leucine, phenylalanine, ornithine, alanine, histidine, norleucine, glutamine, valine, threonine, serine, aspartic acid, beta-cyano alanine, and allothreonine side chains;
- 20 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl, and aralkyl radicals, which radicals are optionally substituted with a group selected from halogen and alkyl radicals, -NO₂, -C≡N, CF₃, -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals;
- 25 R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl,
 30 aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a

disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

5 R⁴ represents radicals as defined by R³ except hydrogen;

R³⁰, R³¹ and R³² represent radicals as defined for R¹, or one of R¹ and R³⁰ together with one of R³¹ and R³² and the carbon atoms to which they are attached form a cycloalkyl
10 radical; and

R³³ and R³⁴ independently represent hydrogen and radicals as defined for R³, or R³³ and R³⁴ together with the nitrogen atom to which they are attached represent
15 heterocycloalkyl and heteroaryl radicals; and

Y and Y' independently represent O, S, and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³.

20 79. Compound of Claim 78 wherein Y and Y' are O.

80. Compound of Claim 78 wherein R¹ represents hydrogen, alkyl, alkenyl, alkynyl, aralkyl, and hydroxyl
25 radicals, and radicals selected from -(CH₂)C(O)CH₃, -CH₂SO₂NH₂, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃) and -C(CH₃)₂(S[O]₂CH₃).

30 81. Compound of Claim 78 wherein R¹ represents alkyl radicals having from 1 to about 4 carbon atoms and alkenyl radicals having from 3 to 8 carbon atoms.

82. Compound of Claim 78 wherein R¹ represents
35 hydrogen, methyl, ethyl, isopropyl, propargyl, t-butyl, sec-butyl, benzyl and phenylpropyl radicals.

83. Compound of Claim 78 wherein R¹ and R³¹ are both hydrogen and R³⁰ and R³² are both methyl.

84. Compound of Claim 78 wherein R¹, R³⁰, R³¹ and R³² are selected from hydrogen and methyl radicals.

85. Compound of Claim 78 wherein R¹ is methyl and R³⁰, R³¹ and R³² are hydrogen.

86. Compound of Claim 78 wherein R³⁰ is hydrogen and R¹, R³¹ and R³² are methyl.

87. Compound of Claim 78 wherein R¹ and R³¹ are hydrogen and R³⁰ and R³² together with the carbon atoms to which they are attached form a three- to six-membered cycloalkyl radical.

88. Compound of Claim 78 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals, and -C \equiv N, CF₃, and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents alkyl radicals.

89. Compound of Claim 78 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals.

90. Compound of Claim 78 wherein R² represents aralkyl radicals.

91. Compound of Claim 78 wherein R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

92. Compound of Claim 78 wherein R² represents an n-butyl and iso-butyl radicals.

93. Compound of Claim 78 wherein R² represents benzyl, 4-fluorobenzyl, and 2-naphthylmethyl radicals.

94. Compound of Claim 78 wherein R² represents
5 a cyclohexylmethyl radical.

95. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl, haloalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
10 heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

96. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl and aryl radicals.
15

97. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl and alkenyl radicals.

98. Compound of Claim 78 wherein R³ and R⁴ independently represent alkoxyalkyl and hydroxyalkyl radicals.
20

99. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl, cycloalkyl and
25 cycloalkylalkyl radicals.

100. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.
30

101. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl, aryl and aralkyl radicals.

102. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl, cycloalkyl,
35 cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

103. Compound of Claim 78 wherein R³ represents alkyl radicals having from about 2 to about 5 carbon atoms and R⁴ represents alkyl and aryl radicals.

5 104. Compound of Claim 96 wherein R⁴ represents methyl and phenyl radicals.

105. Compound of Claim 78 wherein R³ and R⁴ independently represent alkyl radicals having from about
10 2 to about 5 carbon atoms, cycloalkylalkyl radicals, aryl and aralkyl radicals, heterocycloalkylalkyl radicals, heteroaryl and heteroaralkyl radicals.

106. Compound of Claim 78 wherein R³
15 represents benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl, and 2-naphthylmethyl radicals and R⁴ represents a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

20 107. Compound of Claim 78 wherein R³ is cyclohexylmethyl and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

25 108. Compound of Claim 78 wherein R³ is i-amyl and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

30 109. Compound of Claim 78 wherein R³ is i-butyl and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

35

110. Compound of Claim 78 wherein R³ is n-butyl or n-propyl and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

111. Compound of Claim 78 wherein R³ is cyclohexyl and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

112. Compound of Claim 78 wherein R⁴ represents alkyl radicals.

113. Compound of Claim 78 wherein R⁴ represents aryl and heteroaryl radicals.

114. Compound of Claim 78 wherein R⁴ represents alkyl radicals having from 1 to about 6 carbon atoms..

115. Compound of Claim 78 wherein R³ represents heteroaralkyl radicals and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

116. Compound of Claim 78 wherein R³ is a p-fluorobenzyl radical and R⁴ is a phenyl or substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

117. Compound of Claim 78 wherein R³³ and R³⁴ independently represent hydrogen and alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

118. Compound of Claim 78 R^{33} and R^{34} both represent hydrogen.

5 119. Compound of Claim 78 wherein R^{33} and R^{34} independently represent alkenyl and alkynyl radicals

10 120. Compound of Claim 78 wherein R^{33} and R^{34} independently represent hydroxyalkyl and alkoxyalkyl radicals.

121. Compound of Claim 78 wherein R^{33} and R^{34} independently represent alkyl and aralkyl radicals.

15 122. Compound of Claim 78 wherein R^{33} and R^{34} independently represent cycloalkyl and cycloalkylalkyl radicals.

20 123. Compound of Claim 78 wherein R^{33} and R^{34} independently represent heteroaryl and heteroaralkyl radicals.

25 124. Compound of Claim 78 wherein R^{33} and R^{34} independently represent heterocycloalkyl radicals.

125. Compound of Claim 78 wherein R^{33} and R^{34} together with the nitrogen atom form a heterocyclyl or heteroaryl radical.

30 126. A pharmaceutical composition comprising a compound of Claim 78 and a pharmaceutically acceptable carrier.

35 127. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 126.

128. Method of Claim 127 wherein the retroviral protease is HIV protease.

129. Method of treating a retroviral infection
5 comprising administering an effective amount of a composition of Claim 126.

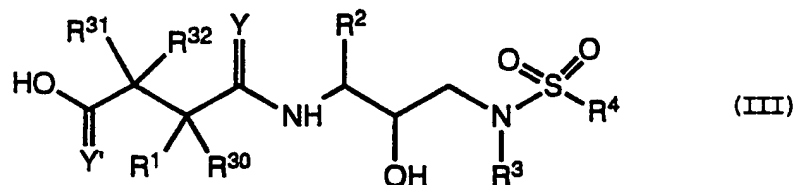
130. Method of Claim 129 wherein the retroviral infection is an HIV infection.

10

131. Method for treating AIDS comprising administering an effective amount of a composition of Claim 126.

15

132. Compound represented by the formula:



or a pharmaceutically acceptable salt, prodrug or ester
20 thereof, preferably wherein;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CO₂CH₃, -CH₂CO₂CH₃,
-CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂,
-CONH₂, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃),
25 -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and
cycloalkyl radicals and amino acid side chains selected
from asparagine, S-methyl cysteine and the corresponding
sulfoxide and sulfone derivatives thereof, glycine,
leucine, isoleucine, allo-isoleucine, tert-leucine,
30 phenylalanine, ornithine, alanine, histidine, norleucine,
glutamine, valine, threonine, serine, aspartic acid, beta-
cyano alanine, and allothreonine side chains;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;

R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical;

Y and Y' independently represent O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³;

R⁴ represents radicals as defined by R³ except for hydrogen; and

R³⁰, R³¹ and R³² represent radicals as defined for R¹, or one of R¹ and R³⁰ together with one of R³¹ and R³² and the carbon atoms to which they are attached form a cycloalkyl radical; or R³⁰ and R³² together with the carbon atoms to which they are attached form a cycloalkyl radical.

133. Compound of Claim 132 wherein Y and Y' are O.

134. Compound of Claim 132 wherein Y and Y' are S.

135. Compound of Claim 132 wherein R¹

represents hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals, hydroxyl radicals, and radicals selected from
- $(\text{CH}_2)\text{C}(\text{O})_2\text{CH}_3$, $-\text{CH}_2\text{SO}_2\text{NH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$,

- 5 $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{CONH}_2$, $-\text{C}(\text{CH}_3)_2(\text{SH})$,
 $-\text{C}(\text{CH}_3)_2(\text{SCH}_3)$, $-\text{C}(\text{CH}_3)_2(\text{S}[\text{O}]\text{CH}_3)$ and $-\text{C}(\text{CH}_3)_2(\text{S}[\text{O}]_2\text{CH}_3)$.

136. Compound of Claim 132 wherein R^1 represents hydrogen, methyl, ethyl, propyl, benzyl,
10 phenyl, propargyl, hydroxyl and radicals selected from
 $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CONH}_2$ and $-\text{CH}_2\text{COOH}$, represented by the
formula $\text{CH}_2\text{C}(\text{O})\text{R}''$ wherein R'' represents $-\text{CH}_3$, NH_2 and
-OH.

- 15 137. Compound of Claim 132 wherein R^1 and R^{31}
are both hydrogen and R^{30} and R^{32} are both methyl.

138. Compound of Claim 132 wherein R^{30} is
hydrogen and R^1 , R^{31} and R^{32} are all methyl.
20

139. Compound of Claim 132 wherein R^{30} , R^{31}
and R^{32} are hydrogen and R^1 is methyl.

140. Compound of Claim 132 wherein R^1 and R^{31}
25 are both hydrogen and R^{30} and R^{32} together with the
carbon atoms to which they are attached form a three to
six-membered cycloalkyl radical.

141. Compound of Claim 132 wherein R^2
30 represents alkyl, cycloalkylalkyl and aralkyl radicals,
which radicals are optionally substituted with halogen
radicals and radicals represented by the formula $-\text{OR}^9$ and
 $-\text{SR}^9$ wherein R^9 represents alkyl radicals.

- 35 142. Compound of Claim 132 wherein R^2
represents alkyl, cycloalkylalkyl and aralkyl radicals.

143. Compound of Claim 132 wherein R^2

represents aralkyl radicals.

144. Compound of Claim 132 wherein R²
represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 2-
5 naphthylmethyl and cyclohexylmethyl radicals.

145. Compound of Claim 132 wherein R²
represents an n-butyl and iso-butyl radicals.

10 146. Compound of Claim 132 wherein R²
represents benzyl, 4-fluorobenzyl, and 2-naphthylmethyl
radicals.

147. Compound of Claim 132 wherein R²
15 represents a cyclohexylmethyl radical.

148. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl, haloalkyl, alkenyl,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl,
20 heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl,
heteroaryl and heteroaralkyl radicals.

149. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl and aryl radicals.
25

150. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl radicals.

151. Compound of Claim 132 wherein R³ and R⁴
30 independently represent alkyl, cycloalkyl and
cycloalkylalkyl radicals.

152. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl, heterocycloalkyl and
35 heterocycloalkylalkyl radicals.

153. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl, aryl and aralkyl radicals.

154. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl, cycloalkyl,
cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl,
5 aryl, aralkyl, heteroaryl and heteroaralkyl radicals.

155. Compound of Claim 132 wherein R³
represents alkyl radicals having from about 2 to about 5
carbon atoms.
10

156. Compound of Claim 132 wherein R³
represents n-propyl, i-butyl, neo-pentyl, n-pentyl,
cyclohexyl, cyclohexylmethyl, n-hexyl, i-amyl, and
n-butyl radicals.
15

157. Compound of Claim 132 wherein R³ and R⁴
independently represent alkyl radicals having from about
2 to about 5 carbon atoms, cycloalkyl, cycloalkylalkyl
radicals, aryl radicals, aralkyl radicals, heteroaryl
20 radicals, heterocycloalkylalkyl radicals and
heteroaralkyl radicals.

158. Compound of Claim 132 wherein R³
represents benzyl, para-fluorobenzyl, para-methoxybenzyl,
25 para-methylbenzyl, and 2-naphthylmethyl radicals and R⁴
represents a phenyl or substituted phenyl radical wherein
said substituents are selected from chloro, fluoro,
nitro, methoxy and amino substituents.

159. Compound of Claim 132 wherein R³ is
cyclohexylmethyl or cyclohexyl radical and R⁴ is a phenyl
or substituted phenyl radical wherein said substituents
are selected from chloro, fluoro, nitro, methoxy and
amino substituents.
30

160. Compound of Claim 132 wherein R³ is i-
amyl or n-butyl and R⁴ is a phenyl or substituted phenyl
radical wherein said substituents are selected from
35

chloro, fluoro, nitro, methoxy and amino substituents.

161. Compound of Claim 132 wherein R³ is i-butyl and R⁴ is a phenyl or substituted phenyl radical
5 wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

162. Compound of Claim 132 wherein R³ is benzyl or p-fluorobenzyl and R⁴ is a phenyl or
10 substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

163. Compound of Claim 132 wherein R³ is neopentyl and R⁴ is a phenyl or substituted phenyl radical
15 wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

164. Compound of Claim 132 wherein R⁴ represents a phenyl or substituted phenyl radical wherein
20 said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

165. Compound of Claim 132 wherein R³ represents heteroaralkyl radicals and R⁴ is a phenyl or
25 substituted phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

166. Compound of Claim 132 wherein R³ is a p-fluorobenzyl radical and R⁴ is a phenyl or substituted
30 phenyl radical wherein said substituents are selected from chloro, fluoro, nitro, methoxy and amino substituents.

35

167. A pharmaceutical composition comprising a compound of Claim 132 and a pharmaceutically acceptable carrier.

168. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 167.

5

169. Method of Claim 168 wherein the retroviral protease is HIV protease.

170. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 167.

10

171. Method of Claim 170 wherein the retroviral infection is an HIV infection.

15

172. Method for treating AIDS comprising administering an effective amount of a composition of Claim 167.

20 173. A compound of Claim 1 which is:

Butanediamide, N⁴-[2-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*),2S*]]-

25

Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo, phenylmethyl ester, [1S-[1R*(S*),2S*]]-

30

- Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-, [1S-[1R*(S*),2S*]]-
- 5 Butanediamide, N⁴-[2-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*),2S*]]-
- 10 Butanoic acid, 4-[[2-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo, phenylmethyl ester, [1S-[1R*(S*),2S*]]-
- 15 Butanoic acid, 4-[[2-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-, [1S-[1R*(S*),2S*]]-
- 20 Butanediamide, N⁴-[2-hydroxy-3-[(3-methylbutyl)(4-methoxyphenylsulfonyl)amine]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*),2S*]]-
- 25 Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo, phenylmethyl ester, [1S-[1R*(S*),2S*]]-
- 30 Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-, [1S-[1R*(S*),2S*]]-
- 35 Butanoic acid, 4-[[2-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-, [1S-[1R*(S*),2S*]]

- Butanoic acid, 4-[[2-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo, phenylmethyl ester, [1S-[1R*(S*),2S*]]-
- 5
- Butanediamide, N⁴-[2-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*), 2S*]]
- 10 Butanediamide, N⁴-[2-hydroxy-3-[(3-methylbutyl)(4-fluorophenylsulfonyl)amine]-1-(phenylmethyl)propyl]-2,2,3-trimethyl-, [1S-[1R*(S*),2S*]]-
- Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(4-fluorophenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo, phenylmethyl ester, [1S-[1R*(S*),2S*]]-
- 15
- Butanoic acid, 4-[[2-hydroxy-3-[(3-methylbutyl)(4-fluorophenylsulfonyl)amino]-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-, [1S-[1R*(S*),2S*]]-
- 20

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 93/07815

| | | |
|---|--|--------------------------|
| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) * | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC | | |
| IPC ⁵ : C 07 C 311/18, C 07 C 311/05, C 07 C 311/29, C 07 K 5/06, A 61 K 37/64, A 61 K 31/325 | | |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched * | | |
| Classification System | Classification Symbols | |
| IPC ⁵ | C 07 C 311/00, A 61 K 13/00, A 61 K 37/00, C 07 K 5/00 | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched * | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT * | | |
| Category * | Citation of Document, ** with indication, where appropriate, of the relevant passages ** | Relevant to Claim No. ** |
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| <p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p> | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report | |
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ANHANG

ANNEX

ANNEXE

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

to the International Search
Report to the International Patent
Application No.

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

PCT/US 93/07815 SAE 78957

In diesem Anhang sind die Mitglieder
der Patentfamilien der im obenge-
nannten internationalen Recherchenbericht
angeführten Patentdokumente angegeben.
Diese Angaben dienen nur zur Unter-
richtung und erfolgen ohne Gewähr.

This Annex lists the patent family
members relating to the patent documents
cited in the above-mentioned inter-
national search report. The Office is
in no way liable for these particulars
which are given merely for the purpose
of information.

La présente annexe indique les
membres de la famille de brevets
relatifs aux documents de brevets cités
dans le rapport de recherche inter-
national visé ci-dessus. Les renseigne-
ments fournis sont donnés à titre indica-
tif et n'engagent pas la responsabilité
de l'Office.

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